Epidemiology and Cancer Registries in the Pacific Basin

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EPIDEMIOLOGY AND CANCER REGISTRIES IN THE PACIFIC BASIN

A Conference

held in

Maui, Hawaii

November 11–14, 1975

Chairman:

Brian E. Henderson

Co-Chairmen:

Donovan J. Thompson
Tomio Hirohata

Sponsored by:

Division of Cancer Research Resources and Centers
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Introduction

The impetus for the First Symposium on Epidemiology and Cancer Registries in the Pacific Basin was the establishment of three cancer centers bordering on the Pacific Ocean (Los Angeles County Hospital/University of Southern California, University of Hawaii, and the Fred Hutchinson, Seattle, Washington). These Cancer Centers have developed notable epidemiologic programs utilizing population-based registries. Identification of migrating populations from Asia and the Pacific Islands is a key tool in their epidemiologic research. Investigators at the three Cancer Centers have been involved in such collaborative studies: Hawaii with Japan in the study of colon, stomach, breast, and prostate cancer; Seattle with close links to Taiwan; and Los Angeles with collaborative studies on breast cancer and nasopharyngeal carcinoma with workers in Japan, Hong Kong, and Singapore. We hoped that the First Maui Conference would provide further stimulus for such joint efforts by bringing together representatives from the major cancer research groups in the Pacific Basin.

At this initial Symposium, considerable time was given to each participant to present the current status of their epidemiologic research and projected programs. In addition, workshops were held on breast, nasopharyngeal, colon, and stomach cancer, sites with a tradition of fruitful research in the Pacific Basin. Finally, one session was devoted to a discussion of immunogenetics in the hope that the use of these new tools of epidemiologic research (e.g., typing of the human leukocyte antigen) on migratory populations would be expanded.

At one level, the accomplishments of this first Symposium are most recognizable in the presentations in this monograph. As a body of information, these manuscripts reflect the tremendous opportunities for etiologic research in this area of the world. Descriptive epidemiologic information is now available from diverse population groups in the Pacific Islands, New Guinea, Australia, and the Philippines. Those responsible for these programs have been provided with the experience of others with similar interests but who are further down the road. The feasibility of analytic epidemiology was apparent, and several groups with the available competence and resources are now informed and interested.

Beyond these presentations, the principal accomplishment of this meeting, as with other meetings, was the many initial encounters between isolated investigators of diverse backgrounds and similar interests in the context of a common goal of etiologic research based on descriptive epidemiologic resources.

Brian E. Henderson

CURRENT STATUS OF INDIVIDUAL CANCER REGISTRIES AND POPULATION-BASED STUDIES

Role of the Cancer Registry [1]

C. S. Muir *and* J. Nectoux [2]

ABSTRACT—The cancer registry can be defined as a facility for the collection, storage, analysis, and interpretation of data on persons with cancer. The possible range of registry activities was discussed in relation to the population-based cancer registry. These activities included service to the medical profession and hence the cancer patient, the provision of information for planning control measures, the evaluation of treatment and of screening programs, the conduct of epidemiologic studies, either directly or indirectly, and the education of the public and the medical profession. The resources of the cancer registry can be used in follow-up for industrial and other cohorts exposed to a variety of agents. Registries must be prepared to meet the problem of confidentiality that might arise when information in the registry is linked with other data sets. The value of a cancer registry increases when it becomes possible to examine and assess time trends. Unfortunately, many cancer registries were not adequately funded or staffed to exploit usefully the data already collected at considerable expense. The three types of staff required to ensure full utilization were discussed.—Natl Cancer Inst Monogr 47: 3–6, 1977.

A cancer registry can be defined as a facility for the collection, storage, analysis, and interpretation of data on persons with cancer. A hospital-based registry performs these functions within the bounds of a hospital or group of hospitals. The population-based registry operates in relation to newly diagnosed cancers in a population of well-defined composition and size. This paper is concerned with the functions of the latter type, although some of these activities also may be undertaken by the hospital-based registry.

SPHERES OF ACTIVITY

The activities of the cancer registry include: service, control planning, treatment evaluation, epidemiology, screening evaluation, and education (*1*). It is unlikely that one registry will encompass all activities, because local circumstances and needs often dictate specific areas of concentration.

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

[2] Unit of Epidemiology and Biostatistics, International Agency for Research on Cancer, 150, Cours Albert-Thomas, 69008 Lyon, France.

CANCER REGISTRY ACTIVITIES

Service

The success of a cancer registry may be determined by the quality of service given the medical profession in patient follow-up and survival computation. Many cancer registries send reminders to practicing physicians that an individual should be seen again on an anniversary date; few contact patients directly for this purpose.

The Hawaii Cancer Registry (Rellahan W: Personal communication) will on demand provide the inquiring physician information about survival in the 5 previous years by stage, ethnic group, and treatment for a particular type of cancer; thus the practicing physician is given an indication of possible appropriate therapy. The provision, on request, of listings of the patients seen by individual clinicians or services is always appreciated.

Cancer registries (by providing centralization of records) assist a physician who is trying to determine previous patient care. The South Metropolitan Cancer Registry (United Kingdom) automatically receives copies of death certificates that mention cancer and sends an abstract of the death certificate to the respective hospital and attending physician, thereby updating and completing patient records. Many central registries assist in the training of record-room and hospital-based registry staff.

Control Planning

The data reported to a cancer registry are valuable in the design of health care delivery systems. When information about cancer and other diseases is made available, relative needs can be assessed; and the number and location of beds that will be required for cancer surgery, chemotherapy, radiation, and rehabilitation can be planned.

The cancer pattern delineated by the registry will indicate the types of treatment facilities needed. In countries where cancer of the nasopharynx is common, emphasis will need to be placed on radiation therapy. Where cancer of the liver is common, facilities for chemotherapy will

need to be reinforced. Varying needs will affect the number and type of personnel required. If the cancer registry is not notified each time the patient is seen, estimates for necessary facilities and staff will be less useful. If the appropriate information is recorded on registry records, physicians, health planners, and health educators will be able to estimate the interval between first symptom and first physician contact, between first physician contact and treatment, the length of stay in the hospital for each type of cancer, and the number of patients with cancer who seek medical treatment. This latter estimate cannot be obtained unless the cancer registry has access to all death certificates on which mention of cancer is made.

Treatment Evaluation

Treatment evaluation is an important part of cancer registry work. The survival rate for various types of cancer according to type of treatment and stage of disease may be determined as part of a controlled clinical trial by interested physicians in association with the cancer registry, or the latter may undertake such analyses alone. Cancer registry evaluation of case management for all persons with cancer, whether treated or not, gives a more representative picture of survival for a population as a whole (*2*) than for a series of patients treated by highly skilled personnel in well-equipped centers. Although the results from such specialized centers may be poorer than those obtained elsewhere (since it is possible that only the poor-risk patient is referred to these centers), these findings may still indicate what remedial action is needed.

Epidemiology

Incidence

The population-based cancer registry enumerates all newly diagnosed cases within the registration area and accumulates information on distribution by anatomical site, sex, and age. In acquiring this basic information, the registry may also record residence, ethnic origin, date and place of birth, occupation, religion, and other data. Part or all of this information may be available for the registration area from the census, which permits the computation of a series of incidence rates. This may be the most important single function of a cancer registry.

Since in most registries a large proportion of reported cases will be histologically confirmed with detailed information on the location of the primary neoplasm available, coding of histology and subsite will be possible.

Depending on the size of the population covered by the registry, regional differences within the registration area may be demonstrated. Some of these variations may give rise to hypotheses that can be tested and analyzed. Others have to be confirmed; i.e., the reported twofold elevation of multiple myeloma incidence in northeast Scotland (*3*) as compared with other parts of the country.

If the registry has been in existence for some time, the staff might be able to examine the accumulated data for time trends (*4*) and to determine whether hitherto unusual histologic types of cancer are being reported for certain sites, e.g., angiosarcoma of the liver or adenocarcinoma of the vagina. This aspect of registry work is discussed in detail elsewhere (*5*).

Case-Control Studies

Most registries will not divulge names of persons who have cancer at a particular site without permission from the attending physician. When permission is granted, the registry information can be used by research workers as a source of material for case-control studies. Because the epidemiologist is usually unable to interview all the patients living in the registration area or indeed to obtain a probability sample of such cases, he should compare the characteristics of particular types of cases from interviews with those of all such cases reported to the registry.

Prospective Studies

The study of cancer risk in selected occupational groups has become increasingly important with the introduction of large numbers of chemicals into the environment. Any possible risk that is not detected by animal testing and other short-term studies, e.g., bacterial mutagenicity, should be discovered as soon as possible before the chemical in question becomes widespread in the general environment. Maximal exposure probably will occur in the factory making the product. The assembly of a cohort of exposed persons is expensive, and follow-up for a period of years is even more costly. If the follow-up can be conducted through the cancer registry, i.e., waiting until the exposed persons appear in the cancer registry records, considerable economy can be effected. However, risk in the exposed has to be compared with that in the remainder of the population. Incidence rates for the general population and possibly the region within the registration area

are therefore essential. Without this information it is impossible to compute the number of cases in question that would have occurred if the exposed population had the same risk as the general population (*5*).

The cancer registry can serve in the follow-up of groups exposed by on-the-job contact and of cohorts with other types of exposure. Thus Clemmesen and colleagues (*6*), realizing that phenobarbitone was a potent enzyme inducer and caused neoplasms in the mouse liver, identified a group of epileptics on long-term treatment with phenobarbitone and determined that they experienced no excess cancer risk. Similarly, groups suffering from such selected diseases as the various manifestations of alcoholism, ulcerative colitis, or multiple polyposis can be followed. Persons with cholesterol metabolism imbalance evidenced by chronic cholecystitis and gallstones could be followed to determine whether their metabolic condition is associated with a greater risk of neoplasia.

Migrant Studies

If the place of birth of migrants with cancer is recorded and their number in the population of the host country is made available from censuses, then studies of migrants may be undertaken (*7*). This type of data has been most important in demonstrating the probable environmental causation of numerous cancers for which the precise etiology is not yet known, e.g., cancer of the colon (*8*).

Screening Evaluation

Public pressure to provide screening and early detection facilities is considerable. The cancer registry staff can assist in the evaluation of the efficacy of these facilities by studying the proportion of cancer at a given site that is reported, by stage, through the screening program and other routes and then estimating survival for both groups. If screening is truly effective and morbidity is constant, the mortality rate should decrease (*9*). The cost may be assessed in relation to the benefit derived from these programs.

Education

The cancer registry may embark on a program of public education or provide the basic material to the local cancer society and professional organizations. If the cancer registry decided to launch such programs, as the New Mexico Registry did, the material released could contain announcements on new cancer hazards, data on cancer problems in the regions served by the registry, and a yearly outline of the pattern and trends of cancer.

Professional education may be oriented to detailed comment on recent advances and trends. Since the average general practitioner in the United States with a clientele of about 3,000 patients will not see more than 8 to 10 persons with cancer each year, the more basic educational material should also be sent to him.

PROBLEMS

Cancer registries are not without problems (*10*). The accusation that they have become graveyards for dead statistics is (unfortunately) at least partially true; this cannot be otherwise until cancer registries are adequately funded and staffed with data collectors, recordkeepers, analysts, and interpreters. Funding must extend for a long period; with each advancing year, the value of the registry increases, and examination and assessment of time trends are possible.

Staffing

Cancer registries have evolved in different ways. Some, as the one in Singapore, began as a collection of data on cancer cases that were confirmed by histologic examination in a pathology laboratory. The registries have gradually become population based. Others have been affiliated with medical schools or health service systems from their beginning, and some started in governmental statistics offices. These diverse origins often resulted in different staffing patterns that are often difficult to change, even though the scope of work undertaken may have changed considerably.

To be really effective, a cancer registry requires three types and levels of staff. 1) Bookkeepers, clerks, and secretarial assistants must conscientiously check incoming data for completeness and cross-reference files to see if the patient was previously reported. These individuals often acquire a remarkable intuition and are able to spot matches that might be overlooked by less-experienced staff or by a computer. 2) Analysts, often using a computer, check the data for internal consistency and again for completeness and then prepare appropriate tabulations. The tabulations may be routine, e.g., for the annual report, or be prepared to meet a specific need of registry staff and research and other workers. 3) Interpreters, often trained in epidemiology (who by virtue of

their association with the registry and their participation in the day-to-day work), provide considerable insight into the strengths and weaknesses of the material. These staff levels, although complementary, are distinct and require different temperaments and background. All three levels are properly represented in few cancer registries.

Adequate staffing means adequate funding. As a rule of thumb, for passive registration (i.e., the registry waits for reports to come in), a staff of five would be required for a population of 1 million. For active registration, this figure should be doubled. If the registry staff is to be actively employed in follow-up, then a larger staff would normally be required. Like any other organization, there is a critical mass, probably of the order of 8–10 persons, for efficient operation.

Confidentiality

Cancer registries constitute one of the earliest forms of data banks and therefore face the increasing public awareness of the problems of confidentiality inherent in the existence of such banks. Unfortunately, the activities of credit and security organizations have come to be associated in the public mind with those of other data-collecting organizations, such as the cancer registries or census authorities. The fear of 1984 is real. Cancer registries must be prepared to meet this problem by ensuring that not only do mechanisms for confidentiality exist, but that the public knows they exist. If research is conducted by the epidemiologic staff of a cancer registry, then these fears should be allayed.

As previously mentioned, the cancer registry is a cheap and effective way of following cohorts exposed to various risks. For this to be effective and economical implies the presence on both sets of data of sufficient identifying information to permit an unequivocal match. Not all countries have issued their citizens the unique personal identification numbers that facilitate this task. With regard to confidentiality, where such numbers exist, strict rules concerning the matching of two or more data sets are in existence (*11*).

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Cancer Registries in Japan: Activities and Incidence Data[1,2]

Isaburo Fujimoto, *M.D.*,[3] Aya Hanai, *B.Sci.*, Fumio Sakagami,[3] Toshio Shigematsu, *M.D.*,[4] Akira Takano, *M.D.*,[5] Reiko Inoue, *P.H.N.*,[6] Michihiro Nishida, *M.D.*,[7] *and* Iwao Senoh[8]

ABSTRACT—Population-based cancer registries are operating in 16 of 49 prefectures in Japan. This paper deals with the studies on cancer registries conducted by the research group supported by the Ministry of Health and Welfare during 1972–74. The organization and activities of every prefecturewide cancer registry were surveyed in 1973. Present status and difficulties in registry operation were observed. To stimulate the registry activities, "Guidelines for Population-based Cancer Registration" was published. In 1974, incidence data were collected from six prefectures on standard forms to compare them with one another. Using these data, we estimated cancer incidence rates in Japan. Incidence for all sites was 183/100,000 population in males and 159 in females. Most prevalent site in males was the stomach, followed by the lung and liver. In females, the most frequent type observed was again cancer of the stomach, followed by uterus, breast, liver, and lung. Age-specific incidence rates were also presented by site and sex. Trend of age-adjusted incidence rates was observed during 1963–71 in Osaka. Marked increase of incidence rates was noticed in cancers of the colon, lung, and pancreas. Decrease also was observed in the incidence of cancers of the stomach, esophagus, and liver. In 1975, a new research group was organized. They have been trying to standardize registry operation, using registry data and organizing a nationwide registry network in Japan.—Natil Cancer Inst Monogr 47: 7–15, 1977.

In Japan, population-based cancer registration operates in 16 prefectures and two cities as of 1975; three kinds of morbidity surveys have been conducted. However, it is regrettable that all these programs were conducted quite independently of one another until 3 years ago.

Two research groups on cancer registration were organized in 1972. The first group, in which we participated, with Isaburo Fujimoto, M.D., as the group leader, was supported by a research grant from the Ministry of Health and Welfare. The second, with Kazuhiko Irie, M.D., as Chairman, was funded by the Japan Cancer Society. Eight registries participated in the first group and four in the second. These two groups worked in close cooperation, and in June 1975, they were succeeded by a new research group with Isaburo Fujimoto, M.D., as Chairman, under a research grant from the Ministry of Health and Welfare. Thirteen registries are now participating.

Cooperative studies were conducted by the first research group during 1973–74. The organization and activities of every prefecturewide cancer registry were surveyed (1973). After this survey, a conference was held for representatives from all registries to discuss their common problems. For promotion of their activities, "Guidelines for Population-based Cancer Registration" (*1*) was published, in cooperation with all registries and related specialists. Then cancer incidence data were collected from six registries on standard forms, and nationwide incidence was estimated (1974).

The second research group was organized by new registries except that in Hyogo. Therefore, their major activities were focused on the study of the methods for collecting more complete cancer reports.

This report deals with the present status of cancer registration in Japan and the incidence data obtained through studies by the first research group.

PRESENT STATUS OF CANCER REGISTRATION

Historical Review and the Present Organization of Registries

Table 1 shows the date of beginning, population coverage, and the organizational features of each registry; and text-figure 1 gives the geographic location of these prefectures and cities. Numbers given in text-figure 1 correspond to the serial numbers in table 1. In Japan, cancer registration systems presently are in operation in 16 of 47 prefectures (34%). They cover 44% of the entire Japanese population.

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

[2] Supported by a research grant from the Ministry of Health and Welfare, Japan, during 1972–74.

[3] Osaka Cancer Registry, Division of Field Research, Center for Adult Diseases, Osaka, 1–3–3 Nakamichi, Higashinari-ku, Osaka 537, Japan.

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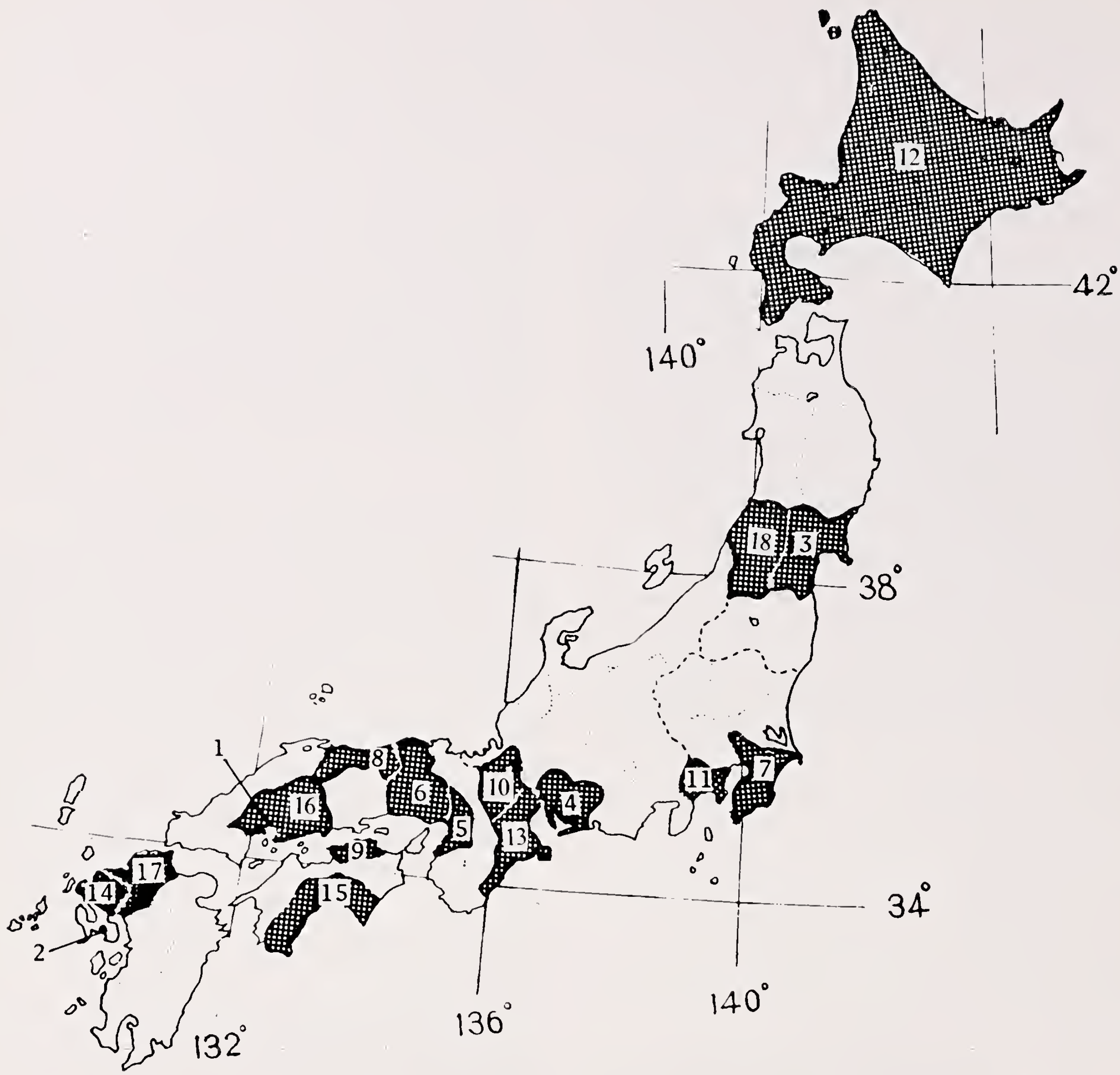
[5] Miyagi Tumor Registry, Miyagi Cancer Society, 6–2–81 Uesugi, Sendai, Miyagi 980, Japan.

[6] Kanagawa Cancer Registry, Kanagawa Adult Diseases Center, 54, Nakao-machi, Asahi-ku, Yokohama 241, Japan.

[7] Hyogo Cancer Registry, Hyogo Prefecture Cancer Center, 7–13 Kusunoki-cho, Ikuta-ku, Kobe, Hyogo 650, Japan.

[8] Okayama Prefecture, Department of Health, 2–4–6 Uchisange, Okayama 700, Japan.



Text-figure 1.—Population-based cancer registries and their location in Japan. Numbers of cities and prefectures correspond to those shown in table 1.

The first and the second registries in table 1 (Hiroshima City and Nagasaki City Registry) were started under the support of a research grant from the Atomic Bomb Casualty Commission (ABCC). The third, Miyagi Prefecture Registry (2), was established by Dr. Mitsuo Segi and had no financial support from the prefectural government until 1971, when the Prefecture took the responsibility for the registration. All other registries, directly responsible to the health department or not, were supported financially from the beginning by their prefectural government.

Responsible organizations and the location of each registry are also indicated in table 1. In six prefectures, the central registry is located in the prefectural cancer center, adult disease center, or in the university. In these instances, the registries are extremely active because assistance is easily

TABLE 1.—*Population-based cancer registration in Japan*

Serial No.	Area covered[a]	Population in 1971, in thousands	Starting date	Organizations responsible	Location of registry
1	Hiroshima (city)	507	May 1957	Hiroshima City Medical Association	ABCC
2	Nagasaki (city)	430	May 1957	Nagasaki City Medical Association	ABCC
3	Miyagi	1,834	Jan. 1959	Tohoku University, Department of Public Health	Tohoku University, Department of Public Health
			April 1972	Prefectural Health Department	Prefectural Adult Diseases Center
4	Aichi	5,466	March 1962	Prefectural Health Department	Prefectural Health Department
5	Osaka	7,624	Dec. 1962	Osaka Medical Association	Prefectural Adult Diseases Center
6	Hyogo	4,665	Jan. 1964	Prefectural Cancer Center	Prefectural Cancer Center
7	Chiba	3,511	April 1964	Prefectural Health Department	Prefectural Health Department
8	Tottori	567	Jan. 1969	Tottori Medical Association	Tottori University, Department of Public Health
9	Kagawa	915	April 1969	Prefectural Health Department	Prefectural Health Department
10	Shiga	902	Sept. 1969	Prefectural Health Department	Prefectural Health Department
11	Kanagawa	5,655	Jan. 1970	Kanagawa Medical Association	Prefectural Adult Diseases Center
12	Hokkaido	5,679	April 1972	Hokkaido Health Department	Hokkaido Health Department
13	Mie	1,549	April 1972	Mie Cancer Society	Mie Cancer Society
14	Saga	831	Jan. 1973	Prefectural Health Department	Prefectural Health Department
15	Kochi	784	Jan. 1973	Kochi Medical Association	Kochi Medical Association
16	Hiroshima	2,460	April 1973	Hiroshima Medical Association	Hiroshima Medical Association
17	Fukuoka	4,022	July 1973	Cancer Research Committee	Cancer Research Committee
18	Yamagata	1,198	Aug. 1974	Yamagata Medical Association	Prefectural Adult Diseases Center

[a] Area is a prefecture, unless otherwise indicated.

available from the technical staff. However, when a central registry is located in the health department of the prefectural government, activities are usually limited. Six registries of this type are in operation; two of them are now planning to move into the prefectural cancer center.

Morbidity Survey in Japan

Three morbidity surveys have been done in Japan. In 1959 one (*3*) conducted in four prefectures (Miyagi, Ishikawa, Yamaguchi, and Kumamoto), was sponsored by the Ministry of Health and Welfare. This is the only national survey to obtain data on cancer incidence, which was calculated on the basis of reports received from hospitals and general practitioners.

Another morbidity survey has been repeated by the Okayama Prefectural Government (*4*) four times every 3 or 4 years since 1968. A third morbidity survey in Okinawa Prefecture (*5*) was done in 1967–68 in cooperation with the Okinawa Medical Association and the National Cancer Center. In these surveys, cancer death certificates and cancer reports were used for calculating incidence.

Source of Information for Registration

In Japan, the registries collected cancer reports not only from hospitals but also from general practitioners because 30% of the patients with neoplasms were never admitted to hospitals (*6*).

Death certificates also were collected in 10 of 16 registries via prefectural governments or health centers. In the 10 registries, reports and death certificates were collated to obtain as complete information as possible. The remaining six registries worked with reports only, but two are now planning to collect data from death certificates.

Seven registries requested reports only of malignant neoplasms [International Classification of Diseases (ICD) No. 140–209]. In eight registries, carcinoma in situ of the uterus was added to reportable tumors. However, Mie Registry requested reports only of stomach and esophagus cancers.

Hiroshima Prefecture Registry, a pathology registry, requested that all hospitals send them histology slides of all types of neoplasms. The pathology staff of the registry reexamined all specimens and reported its findings to the doctors who sent the slides.

Eight registries used two types of reports: one for inpatients and the other for outpatients of hospitals and private clinics. The remaining seven registries prepared only one type of reporting form for all cases.

Some Practical Use of Registry Data

Five of the nine prefectural registries that functioned for more than 5 years calculated and published cancer incidence data. Four of the five, and one other, investigated current status of cancer care. Information services were provided

by two registries, which send information about prognoses of the patients on the request of participating hospitals or clinic doctors.

Evaluation of mass screening programs for gastric cancer was conducted by four registries. Names of the people once screened by the program were collated with the master file of cancer cases. Their cancer incidence and mortality were observed 3 to 6 years after screening (average of 4.5 yr). It was proved that stomach cancer mortality among those screened was lower than among the general population. Cases overlooked by the screening program were investigated also in these studies.

Difficulties in Registry Operation

From the survey on registry operation, the following difficulties appeared common to all registries:

1) Reporting rate from hospitals and practitioners' offices was still insufficient.

2) Quality control of the registry work and practical application of the collected materials were not satisfactory because of the shortage of staff and budget.

3) No registry except Tottori had a follow-up program of registered cases.

These difficulties were due to the following:

1) Many people still regarded the work of the central registry as a simple clerical function, not appreciating the sophisticated technique and knowledge necessary to establish and maintain a cancer registration system.

2) The budget of most of the central registries was inadequate, and the staff was limited in quality and quantity.

3) Few Japanese hospitals had cancer registries or central medical record libraries. Thus in most hospitals, reporting depended on the effort of individual doctors.

4) Prefecturewide cancer registration was not given any financial or administrative support from the Ministry of Health and Welfare until March 1972. All the registries have been supported primarily by the prefectural government.

In 1973, after a panel discussion by the representatives of all registries in Japan, the following decisions were made:

1) To organize a nationwide association of registries,

2) To establish "guidelines for cancer registration,"

3) To collect and publish the data from existing registries on a uniform basis, and

4) To explore feasibility of the practical use of the registry data.

Publication of "Guidelines"

Because of deficiencies existing among the registries in operational methods, information sources, reportable items, methods of calculating incidence, etc., we felt it necessary to establish a set of guidelines. In January 1975, we published "Guidelines for Population-based Cancer Registration" (*1*), in which we tried to include various opinions from all registries and many specialists. This publication was not intended as a hasty standardization of the activities of all registries, as we felt it more desirable at this stage that each registry try to develop its own pattern. The booklet was, therefore, intended to help registries in organizing their activities.

ESTIMATION OF CANCER INCIDENCE IN JAPAN

No national cancer survey had been conducted in Japan since 1959. In 1974, representatives of five registries decided to collect their data on standard forms, to compare them with one another, and to estimate cancer incidence in Japan. Data from the Okayama Prefecture were included in this program; a periodic cancer survey had been repeated in this area.

Participating Registries and Method of Calculation

Table 2 shows the names of participating registries, survey periods, number of cancer cases, and census population of 1970. The population included was 21.8 million, corresponding to 21% of Japan's total population. The observed number of cases reached 59,451. To estimate cancer incidence in Japan, we did not use data from Hyogo because the completeness of reporting was inadequate.

The first step was to estimate age-specific incidence rates for all Japan. The mean of the rates from the five prefectures (not including Hyogo) was calculated. We did not divide the total number of cases by the total population of these five prefectures because it would have obscured certain characteristic variations among the prefectures.

Average incidence rates by specific age group and by sex for each site were multiplied by the population of the corresponding age group of all Japan. The sum of the number of calculated cancer cases of each age group was divided by the total national population. This procedure,

TABLE 2.—*Prefectures, survey period, number of cancer cases, and population*

Prefecture	Survey period	No. of cancer cases			Population (census of 1970)		
		Total	Male	Female	Total	Male	Female
Miyagi	1968–71	11,236	6,024	5,212	1,819,223	889,036	930,187
Kanagawa	1970	7,368	3,901	3,467	5,472,247	2,822,212	2,650,035
Osaka	1970–71	21,313	11,493	9,820	7,620,480	3,823,622	3,796,858
Hyogo	1971–72	13,415	7,330	6,085	4,667,928	2,299,961	2,367,967
Tottori	1969–70	2,541	1,322	1,219	567,405	268,801	298,604
Okayama	1969	3,578	1,794	1,784	1,707,026	819,359	887,667
Total		59,451	31,864	27,587	21,854,309	10,922,991	10,931,318

employed for each site and sex, was used to estimate cancer incidence.

The world population presented by Doll et al. (7) was used as the standard population in calculating age-adjusted incidence and mortality rates.

Completeness and Accuracy of Registry Data

The proportion of the cases registered by death certificate only was regarded as an inverse index of the completeness of cancer incidence data. In most registries, the proportion ranged from 25 to 45% (table 3). These percentages were regrettably high, reflecting the fact that the hospital-based cancer registry was not yet developed in Japan.

The proportion of the cases confirmed by histologic examination is also shown in table 3. The percentage varied between 19% and 46%, which was much lower than those of the registries in Europe and the United States. Some possible explanations for this finding are: Distribution of cancer by site is quite different from that in many other countries, making histologic tests more difficult; the tests are covered insufficiently by health insurance; and a shortage of clinical pathologists exists.

Cancer Mortality and Morbidity in the Six Prefectures

Cancer mortality and morbidity in six prefectures were calculated at the Osaka Cancer Registry. The results are shown in table 4.

TABLE 3.—*Percentage of the cases registered by death certificate only and cases confirmed by histologic examination, all sites*

Prefecture	Cases registered by death certificate only, %		Cases confirmed by histologic examination, %	
	Male	Female	Male	Female
Miyagi	30.7	26.1	39.0	46.5
Kanagawa	45.7	39.5	21.4	30.6
Osaka	34.9	31.4	29.7	37.4
Hyogo	62.1	54.8	19.4	29.3
Tottori	31.2	27.5	23.7	32.7
Okayama	9.5	9.2	30.4	42.9
Average [a]	30.4	26.7	28.8	38.0

[a] Values given do not include Hyogo.

Age-adjusted incidence rates for selected cancer sites by each registry are shown in table 5. Cancer of the esophagus showed a high rate in both sexes in Miyagi and a low rate in Tottori. However, stomach cancer was most frequent in Tottori.

In males, incidence of cancer of the rectum was highest in Kanagawa and that of the lung, in Osaka. In females, incidences of cancers of the breast and uterus were high in Okayama. This might be partially attributable to the fact that the Okayama survey was for a single year (7).

Cancer Incidence in Japan

The average of crude death rates in these prefectures was compared with mortality rates

TABLE 4.—*Crude and age-adjusted rates of incidence and deaths, all sites*

Prefecture	Crude rates				Age-adjusted rates			
	Incidence		Deaths		Incidence		Deaths	
	Male	Female	Male	Female	Male	Female	Male	Female
Miyagi	169.4	140.1	135.7	99.5	185.1	127.7	148.6	91.8
Kanagawa	138.2	130.8	100.2	85.9	204.0	149.7	151.3	100.3
Osaka	150.3	129.3	113.4	89.3	207.4	142.6	157.7	99.5
Hyogo	159.4	135.2	132.3	98.3	173.9	125.7	145.6	91.3
Tottori	245.9	204.1	184.2	137.5	205.3	153.2	151.8	99.7
Okayama	219.0	201.0	151.2	103.5	183.9	160.4	124.0	78.1

TABLE 5.—*Age-adjusted incidence rates per 100,000 population by selected primary site, sex, and prefecture*[a]

Sex	Prefecture	All sites (140–209)	Esophagus (150)	Stomach (151)	Colon (153)	Rectum (154)	Liver (155, 1978)	Pancreas (157)	Lung (162)	Breast (174)	Uterus (180–182, 2340)	Bladder (188)	Leukemia (204–207)
Male	Miyagi	185.1	12.9	84.0	5.6	6.8	9.4	7.2	20.0	0.2	—	3.7	4.6
	Kanagawa	204.0	10.8	86.6	6.6	8.2	11.3	7.0	21.4	0.1	—	5.8	5.1
	Osaka	207.4	9.7	91.1	6.3	6.9	16.3	5.9	23.5	0.2	—	5.2	4.1
	Hyogo	173.9	7.9	74.4	5.4	6.0	—	5.6	22.3	0.2	—	3.2	3.9
	Tottori	205.3	3.8	108.0	5.2	5.9	18.0	5.1	17.3	0.1	—	4.4	3.8
	Okayama	183.9	4.6	90.2	5.0	7.0	—	3.8	17.5	0.4	—	5.4	4.0
Female	Miyagi	127.7	4.1	39.7	5.3	5.0	4.5	4.4	6.9	12.7	23.9	1.4	3.7
	Kanagawa	149.7	1.9	48.4	6.2	6.3	6.2	4.7	6.9	13.1	24.7	2.7	3.5
	Osaka	142.6	2.8	45.1	5.0	4.6	7.3	3.0	6.7	12.0	28.9	1.2	3.1
	Hyogo	125.7	2.0	38.1	4.2	4.2	—	3.2	6.6	9.5	27.7	1.3	3.0
	Tottori	153.2	1.5	51.7	4.6	6.4	7.7	4.3	5.0	15.7	25.5	2.5	2.6
	Okayama	160.4	2.1	48.3	4.7	5.5	—	2.3	6.7	16.6	34.3	1.4	1.9

[a] *Numbers in parentheses* are ICD numbers.

for all Japan in the Vital Statistics of 1970 (table 6). No differences among them were noticeable, either by site or sex, except for cancer of the bladder (with an average 1.3 times higher than that in the 1970 Vital Statistics), esophagus (0.8 times higher), and leukemia (0.7 times higher). The procedure described in the "Methods" section was used to estimate cancer incidence rates in Japan by site and sex.

Age-specific incidence rates, the mean of the data from five registries, are shown in tables 7 and 8. The estimated numbers of cancer cases and incidence rates for all Japan are indicated in table 9.

Around 1970, cancer incidence rates in Japan were estimated at 183/100,000 population in males and 159 in females. The number of male and female patients was 93,191 and 83,945, respectively, for a total of 177,136. Cancer of the stomach was most prevalent in both sexes. In

TABLE 6.—*Cancer death rates, surveyed prefectures and all Japan*

Primary site (ICD No.)	Male: This survey (average)	Male: All Japan	Female: This survey (average)	Female: All Japan
All sites (140–209)	137.0	132.6	103.2	100.7
Esophagus (150)	6.0	7.3	2.5	2.2
Stomach (151)	60.2	58.6	36.7	36.5
Colon (152, 153)	3.5	3.7	4.3	4.1
Rectum (154)	4.9	5.0	4.1	4.1
Liver (155, 1978)	13.6	11.7	7.0	6.9
Pancreas (157)	5.2	5.0	3.9	3.5
Lung (162)	16.1	14.8	5.6	5.7
Breast (174)	0.2	0.0	4.6	4.7
Uterus (180–182, 2340)	—	—	12.1	12.1
Bladder (188)	2.7	2.0	1.2	1.0
Leukemia (204–207)	2.9	4.0	2.7	3.0

males, cancers of the lung, liver, esophagus, rectum, colon, and pancreas followed (in that order). In females, the second highest rate was for cancer of the uterus, followed by cancer of the breast, liver, lung, rectum, and colon. These were the first figures since 1959 for the national incidence of cancer.

NINE-YEAR TREND OF CANCER INCIDENCE IN OSAKA

Osaka Prefecture had a population of 7,620,480 as of the 1970 census. The capital city of Osaka is surrounded by 28 satellite cities, 15 towns, and 2 villages. Four medical schools, 435 hospitals, and 5,788 private clinics were located there. The number of practicing physicians totaled 10,174 in 1971.

Cancer incidence rates for every 3-year period from 1963 in Osaka are indicated in table 10 and the age-adjusted incidence rates in table 11. Table 12 gives the ratio of age-adjusted incidence in the second and third survey periods against the incidence in the first 3 years, 1963–65.

Cancer incidence trends in table 12 indicate a marked increase in colon cancer during the 9-year period. The incidence of pancreas and lung cancer also increased. However, incidence of cancer of the uterus decreased continuously. In 1969–71, it was 30% lower than in 1963–65. A decrease also was observed in the incidence of cancers of the stomach, esophagus, and liver, as well as cancer in general.

DISCUSSION AND SUMMARY

Cancer registries are developing in Japan, but at present they have limited capacities. However, organization of two research groups during 1972–74 seems to have greatly stimulated activities of

TABLE 7.—*Age-specific incidence rates/100,000 population (male)* [a]

Age, yr	All sites	Buccal cavity and pharynx	Esophagus	Stomach	Colon	Rectum	Liver	Pancreas	Larynx	Lung	Bone	Skin	Prostate	Bladder	Leukemia
	(140–209)	(140–149)	(150)	(151)	(153)	(154)	(155, 1978)	(157)	(161)	(162)	(170)	(172, 173)	(185)	(188)	(204–207)
0–4	13.3	0.1	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.1	0.0	0.1	0.1	5.2
5–9	7.6	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	4.1
10–14	8.8	0.0	0.0	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.1	0.0	0.0	2.6
15–19	10.5	0.0	0.0	0.7	0.0	0.2	0.1	0.0	0.0	0.4	2.3	0.1	0.0	0.0	3.1
20–24	13.4	0.1	0.0	1.1	0.9	0.2	0.2	0.1	0.0	0.2	1.5	0.0	0.1	0.1	2.1
25–29	23.1	0.5	0.0	8.0	1.0	1.7	2.3	0.5	0.0	0.3	0.1	0.5	0.0	0.1	1.8
30–34	30.2	1.4	0.1	12.6	0.7	1.4	1.0	0.6	0.0	1.5	0.5	0.1	0.0	0.1	4.1
35–39	58.7	1.0	0.2	31.2	1.3	2.2	2.4	1.0	0.1	1.7	1.0	1.4	0.0	0.6	2.7
40–44	107.7	2.5	1.7	56.2	3.8	4.5	5.6	2.5	0.9	4.9	0.2	0.7	0.6	1.5	3.8
45–49	194.1	4.1	4.3	102.4	7.3	5.3	16.4	5.6	2.0	10.2	1.6	0.8	0.3	4.8	5.6
50–54	320.5	8.2	5.9	167.0	9.7	10.2	28.0	10.1	4.3	27.7	2.2	2.0	0.6	7.4	5.5
55–59	506.4	9.2	18.5	260.3	10.6	16.1	35.7	16.9	11.4	44.6	3.2	5.1	4.0	12.4	8.6
60–64	794.8	13.6	37.9	399.5	19.7	27.6	50.5	25.4	11.8	91.5	3.6	4.6	6.2	15.5	6.9
65–69	1,146.2	20.8	48.2	539.8	35.2	36.5	75.3	39.4	27.1	150.4	2.7	7.9	20.3	28.1	8.5
70–74	1,551.5	25.0	96.2	696.9	47.4	62.0	107.9	49.4	22.6	190.2	6.2	14.5	35.4	42.4	11.2
75–79	1,742.3	30.7	102.4	782.0	46.1	62.8	126.7	43.9	35.1	212.2	9.2	18.8	50.4	51.9	8.6
80–84	1,724.6	12.2	134.8	721.9	59.5	92.0	127.5	38.2	24.5	167.2	10.2	30.0	89.1	65.7	8.5
Over 85	1,431.7	7.4	70.2	539.5	68.5	60.6	131.6	36.3	27.9	135.7	22.7	18.0	84.3	83.2	0.0
Age-adjusted	197.1	3.4	8.3	92.0	5.8	6.9	13.6	5.8	3.2	19.9	1.5	1.6	3.2	4.9	4.3

[a] *Numbers in parentheses* are ICD numbers.

TABLE 8.—*Age-specific incidence rates/100,000 population (female)* [a]

Age, yr	All sites	Buccal cavity and pharynx	Esophagus	Stomach	Colon	Rectum	Liver	Pancreas	Larynx	Lung	Bone	Skin	Breast	Uterus	Ovary and other female genital organs	Bladder	Leukemia
	(140–209)	(140–149)	(150)	(151)	(153)	(154)	(155, 1978)	(157)	(161)	(162)	(170)	(172, 173)	(174)	(180–182, 2340)	(183)	(188)	(204–207)
0–4	9.9	0.1	0.0	0.0	0.1	0.0	0.7	0.0	0.0	0.1	0.6	0.0	0.0	0.1	0.5	0.0	4.00
5–9	7.1	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.1	0.0	3.0
10–14	6.2	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.4	0.6	0.0	0.1	0.1	1.0	0.1	1.6
15–19	1.0	0.1	0.0	0.9	0.1	0.1	0.0	0.0	0.0	0.4	0.8	0.0	0.4	0.2	1.2	0.0	2.5
20–24	13.5	0.3	0.0	2.7	0.5	0.1	0.2	0.0	0.0	0.1	0.8	0.0	0.2	1.0	1.5	0.0	2.1
25–29	26.9	0.3	0.0	7.9	0.4	1.6	0.8	0.1	0.0	0.2	0.2	0.1	3.9	3.5	1.0	0.1	1.9
30–34	54.7	0.8	0.0	16.4	0.9	0.5	1.9	0.3	0.0	0.9	0.2	0.2	8.4	14.8	1.2	0.6	1.8
35–39	95.3	0.7	0.5	28.5	2.3	2.4	1.5	2.8	0.1	1.3	0.6	0.3	17.1	30.8	3.0	0.1	1.5
40–44	167.0	1.3	0.6	45.3	3.9	4.3	3.0	1.3	0.1	3.0	0.4	0.8	31.3	55.2	3.5	0.5	3.8
45–49	230.6	2.4	0.9	61.2	5.2	6.1	5.1	3.0	2.0	5.0	1.2	2.2	40.6	67.9	6.3	1.5	3.1
50–54	287.0	1.3	2.5	78.9	5.7	13.2	8.1	5.4	0.5	10.4	0.9	2.9	44.7	87.4	4.7	1.9	3.0
55–59	386.5	3.5	5.3	127.1	12.3	13.5	15.3	7.6	2.7	18.1	0.7	3.5	32.0	88.7	8.8	3.5	2.3
60–64	545.0	7.0	10.0	177.9	19.3	16.9	27.3	17.1	1.8	27.6	1.2	4.3	47.7	93.4	11.0	7.3	7.9
65–69	677.0	5.2	13.4	235.8	30.8	35.6	30.9	26.2	3.6	44.0	2.3	3.5	39.3	108.2	8.3	16.9	3.8
70–74	840.8	10.0	22.7	320.8	37.1	36.3	58.1	31.2	4.5	59.3	4.5	7.7	31.6	93.5	4.9	15.0	5.0
75–79	968.4	9.3	40.7	369.8	51.0	43.6	72.3	39.8	4.7	48.3	5.4	7.2	29.0	87.5	10.3	18.6	5.4
80–85	982.1	7.4	44.0	397.6	60.4	45.1	76.0	29.5	4.9	54.6	11.2	20.1	17.5	73.0	0.7	22.0	1.9
Over 85	778.3	9.1	31.7	262.1	61.8	53.9	91.4	10.3	3.8	25.5	6.9	21.5	37.5	46.1	14.0	6.5	3.2
Age-adjusted	146.7	1.4	2.5	46.6	5.1	5.6	6.6	3.7	0.6	6.5	0.9	1.2	14.0	28.3	2.9	1.9	2.9

[a] *Numbers in parentheses* are ICD numbers.

TABLE 9.—*Estimated number of cancer cases and incidence rates in Japan*

Primary site	No. of cases		Incidence rates		Percent of total	
	Male	Female	Male	Female	Male	Female
All sites	93,191	83,945	183.0	159.0	100.0	100.0
Esophagus	3,895	1,490	7.7	2.8	4.2	1.8
Stomach	43,659	27,020	85.7	51.2	46.8	32.2
Colon	2,829	3,167	5.6	6.0	3.1	3.8
Rectum	3,296	3,168	6.5	6.0	3.6	3.8
Liver	6,328	3,809	12.4	7.2	6.8	4.5
Pancreas	2,726	2,158	5.4	4.1	3.0	2.6
Lung	9,324	3,681	18.3	7.0	10.0	4.4
Breast	—	7,953	—	15.1	—	9.5
Uterus	—	16,410	—	31.1	—	19.6
Bladder	2,223	1,064	4.4	2.2	2.4	1.4
Leukemia	2,127	1,504	4.2	2.9	2.3	1.8

the participating registries. The following developments have been observed: 1) The percentage of cases registered by death certificate only has been decreasing in each of five registries listed in table 2; 2) collation of reports with death certificates is to be started in two more registries; and 3) several registries, established since 1972, are reporting the incidence and the status of medical care for cancer patients in their prefectures.

The figures on cancer incidence in Japan presented in this report are the first since the national morbidity survey in 1959. The new research group following the two previous ones intends to prepare and publish an annual report of cancer incidence in Japan with the cooperation of many registries. Also, the status of medical

TABLE 10.—*Average annual cancer incidence rates/100,000 population by selected primary site, sex, and survey period, Osaka* [a]

Sex	Survey period	All sites (140–209)	Esophagus (150)	Stomach (151)	Colon (153)	Rectum (154)	Liver (155, 1978)	Pancreas (157)	Lung (162)	Breast (174)	Uterus (180–182, 2340)	Bladder (188)	Leukemia (204–207)
Male	1963–65	148.7	6.9	74.3	2.9	4.8	11.6	3.2	12.8	—	—	—	—
	1966–68	150.2	6.6	72.0	3.9	4.4	11.3	4.0	14.1	—	—	3.3	3.3
	1969–71	150.6	6.4	67.1	4.6	5.1	11.1	4.1	16.2	—	—	3.5	3.5
Female	1963–65	137.8	2.8	44.3	2.9	4.0	7.3	2.0	5.2	10.0	35.7	—	—
	1966–68	134.8	2.9	43.4	3.9	4.3	6.0	2.4	5.5	10.3	33.9	1.6	2.4
	1969–71	131.6	2.6	41.5	4.6	4.2	6.0	2.7	6.0	11.4	28.0	1.3	2.9

[a] *Numbers in parentheses* are ICD numbers.

TABLE 11.—*Age-adjusted cancer incidence rates per 100,000 population by selected primary site, sex, and survey period, Osaka* [a]

Sex	Survey period	All sites (140–209)	Esophagus (150)	Stomach (151)	Colon (153)	Rectum (154)	Liver (155, 1978)	Pancreas (157)	Lung (162)	Breast (174)	Uterus (180–182, 2340)	Bladder (188)	Leukemia (204–207)
Male	1963–65	216.1	10.9	109.2	4.3	7.1	17.1	4.6	19.1	—	—	—	—
	1966–68	211.1	9.7	101.4	5.4	6.1	16.1	5.6	20.7	—	—	5.1	3.7
	1969–71	204.6	9.1	92.2	6.1	6.8	15.3	5.5	22.9	—	—	5.1	4.0
Female	1963–65	160.1	3.5	52.8	3.5	4.7	9.0	2.4	6.3	11.0	39.8	—	—
	1966–68	152.0	3.6	49.8	4.5	4.9	7.2	2.9	6.4	11.0	31.4	2.0	2.5
	1969–71	143.8	3.0	45.7	5.1	4.7	6.8	3.1	6.8	11.8	29.6	1.5	3.1

[a] *Numbers in parentheses* are ICD numbers.

TABLE 12.—*Ratios of age-adjusted rates in the second and third survey period against the rates in the first period by selected primary site and sex, Osaka* [a]

Sex	Survey period	All sites (140–209)	Esophagus (150)	Stomach (151)	Colon (153)	Rectum (154)	Liver (155, 1978)	Pancreas (157)	Lung (162)	Breast (174)	Uterus (180–182, 2340)
Male	1963–65	100	100	100	100	100	100	100	100	—	—
	1966–68	98	89	93	126	86	94	122	108	—	—
	1969–71	95	83	84	142	96	89	120	120	—	—
Female	1963–65	100	100	100	100	100	100	100	100	100	100
	1966–68	95	103	94	129	104	80	120	101	100	85
	1969–71	90	86	87	146	100	76	129	108	107	69

[a] *Numbers in parentheses* are ICD numbers.

care for cancer patients will be reported. The group is succeeding with its efforts to standardize the method of registration. A handbook for standard methods for central registries is being prepared. These activities should facilitate the development of better population-based registries in Japan.

The changes in cancer incidence in Osaka are remarkable, although the period of observation is extremely limited. It will be necessary to ascertain whether such changes have occurred in other prefectures. At the same time, it will be essential to begin epidemiologic study on the causes of these changes.

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Lung Cancer and Air Pollution [1, 2]

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ABSTRACT—The relationship between incidence of lung cancer and the volume of traffic as indicated by auto exhaust concentration was examined; the results, though suggestive, did not yield consistent evidence of the association between them. Traffic jams in Nagoya began 15 years ago, a period that may not be long enough to provide definitive data on the incidence of lung cancer. The high standardized mortality ratio (SMR) of lung cancer was observed in cities with a population of less than 1 million and guns (rural areas) along the coast, although those in the metropolitan areas with populations of more than 1 million were average. The SMR did not correlate with various socioeconomic conditions and industrial air pollution. Meteorologic or geologic conditions and ocean currents were not associated with SMR of lung cancer by city and gun. The population of a gun or of some cities was not large enough to be statistically significant, and the mortality rate of lung cancer was not always stable.—Natl Cancer Inst Monogr 47: 17–22, 1977.

In Japan, the age-adjusted mortality rate for lung cancer has risen four times for males and two-and-a-half times for females from 1955 to 1973. However since 1972, the rate of increase has been diminishing and stabilizing (*1*).

Text-figure 1 shows the standardized mortality ratio (SMR) of lung cancer by prefecture in Japan for 1969–71. Most prefectures, except the three with an SMR more than 120 for females, have similar ratios (*2*). For the last two decades, explosive industrialization in Japan has led to increased industrial air pollution in many districts. Nevertheless, a significant difference in the death rate from lung cancer has not been observed among prefectures with or without highly industrialized areas. On the other hand, age-adjusted mortality rates for lung cancer in 1972 were 24.9/100,000 for males and 8.1 for females in seven metropolitan areas and 15.9 for males and 4.9 for females in rural areas. The rates in cities with populations of less than 1 million are intermediate between those of the metropolitan (population of more than 1 million) and rural areas as shown in table 1 (Aoki K, Shimizu H: Unpublished observations).

We examined the incidence and mortality of lung cancer in Nagoya, a metropolitan area with a population of 2 million, and in Yokkaichi, with a population of 200,000, where industrial air pollution has been extremely high for the last two decades. Deaths from lung cancer were examined in each area of 4 km². The population of each grid square ranges from 4,000 to 60,000 (80 grid squares in Nagoya and 50 in Yokkaichi). The results show no correlation between excess deaths from lung cancer and industrial air pollution or the general location of industries in both areas. In the city of Ise near Yokkaichi, where almost no industrial air pollution has been noted, mortality from lung cancer has been higher from 1967 to 1973 than in Nagoya and Yokkaichi. High mortality of lung cancer in these three cities was observed, particularly in restricted, small areas with flourishing streets or busy towns near railroad stations where traffic volume is high. A case-control study of lung cancer in Ise revealed that lung cancer was high among truck and taxi drivers and among fishermen and/or residents living near the beach. However, any conclusion was hypothetical because our sample was limited to 77 matched pairs (Aoki K, Shimizu H: Unpublished observations).

Another retrospective study was conducted in 1967–72 in Aichi Prefecture, which has a population of 5.5 million. In a review of death certificates, researchers observed a high frequency of lung cancer in persons who drove cars (deliverymen, cab drivers), but the relative risk could not be calculated because the exact denominators of this occupational group, especially in the age group of 55 years and over, were lacking. A significantly high incidence of lung cancer was reported in a small area of Oyagi around an intersection with much traffic volume and many traffic jams for 10 to 15 years. This high incidence diminished within the past 3 years, supposedly because traffic volume decreased due to a new route (*3*). These facts led us to examine the relationship of exposure to auto exhaust and the occurrence of lung cancer and deaths from this

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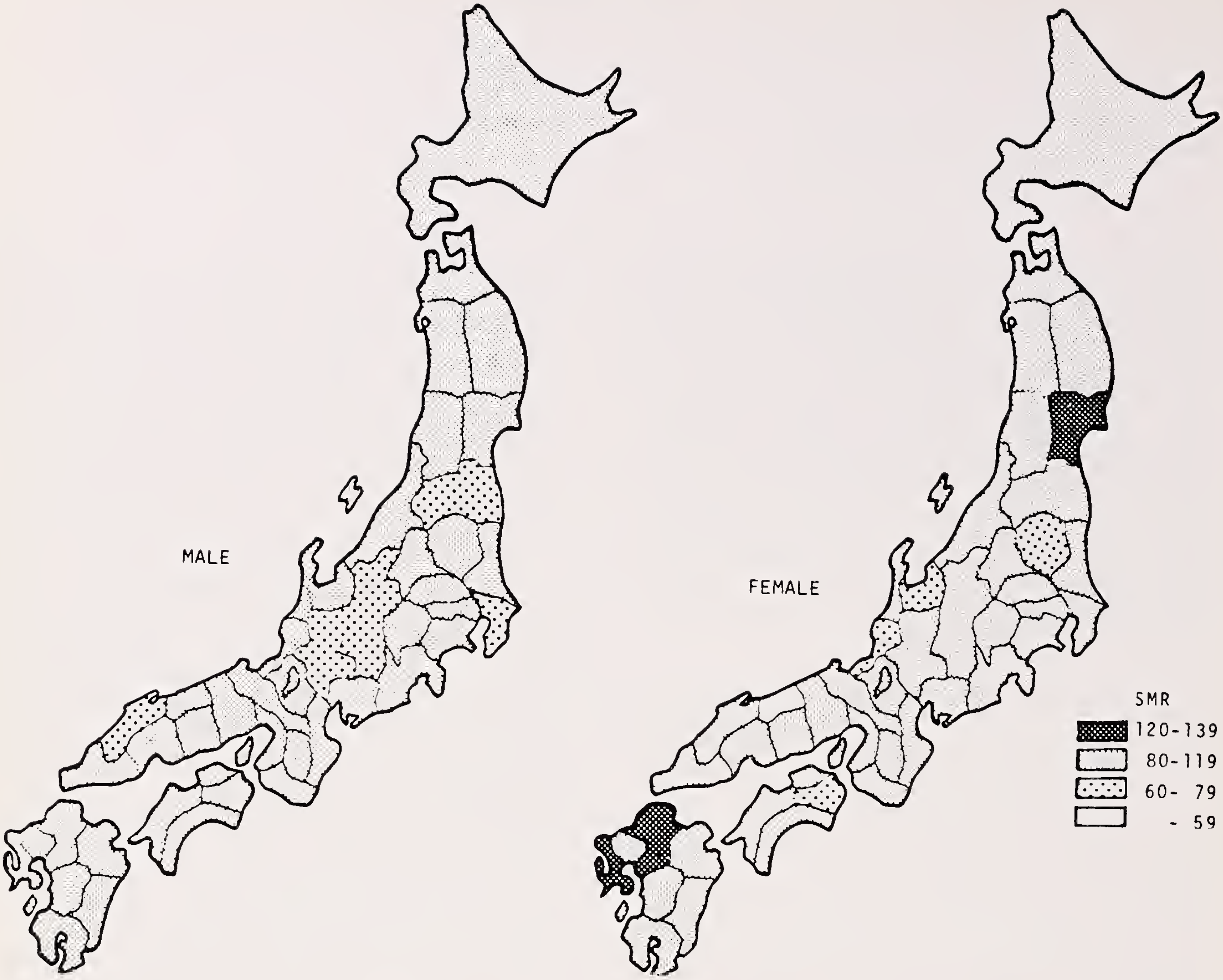


TEXT-FIGURE 1.—Geographic distribution of SMR of lung cancer by prefecture, Japan, 1969–71.

neoplasm among residents of coastal areas of Japan; this paper is a preliminary report.

MATERIALS AND METHODS

Correlation between incidence of lung cancer among the residents of streets with high traffic volume.—Traffic volume was measured by the amount of exhaust from cars. In theory, the amount of carcinogenic substances (ρ) in gas exhaust is proportional to traffic volume K per hour:

$$\rho(R)\,\alpha\,\frac{K}{R^{\alpha}}$$

where R is the distance from the street and α is the diffusion coefficient. The distribution of nitric oxides (NO) and carbon monoxide (CO) concentrations, most of which seemed to be derived from auto exhaust, exponentially diminished and leveled off at distances of 20–30 and 40–70 m, respectively (*4*). The NO or CO concentration was parallel with traffic volume per unit of time.

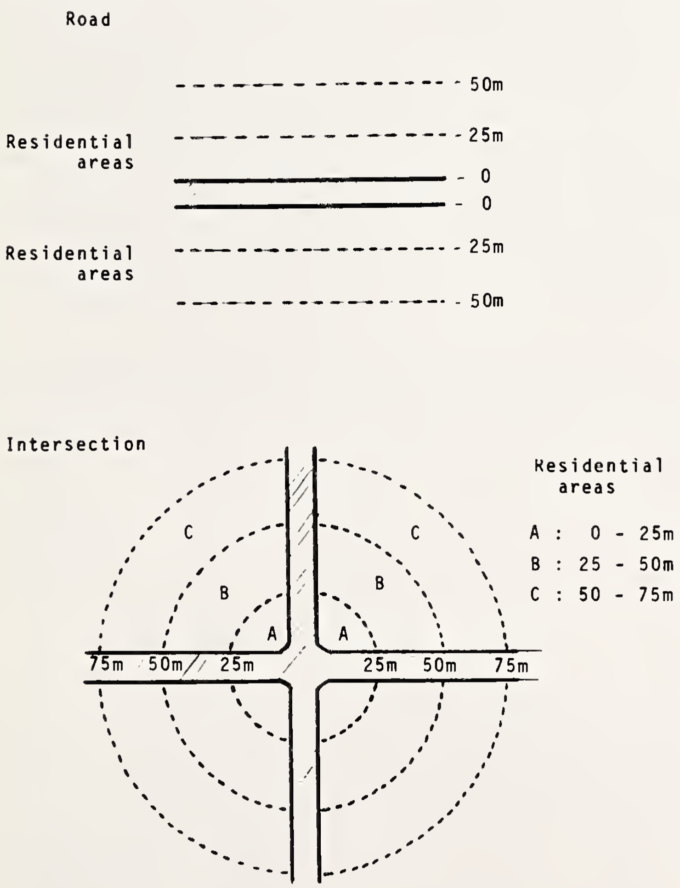
TABLE 1.—*Age-adjusted death rates of lung cancer/100,000 in Japan, 1972*[a]

Sex	Seven metropolitan areas	Cities	Guns (rural area)
Male	24.9	19.5	15.9
Female	8.1	6.2	4.9

[a] Age-adjusted death rates are calculated on the basis of Segi-Doll's rounded standard world population.

The diffusion coefficient is related to the speed of the car, wind velocity, type and amount of housing along the street, and topographic and meteorologic conditions; however, the pattern of diminishing curve of NO or CO concentration did not vary much each day. Therefore, we examined the relationship between traffic volume within a distance of 100 m from the street or intersection and the number of deaths from lung cancer among residents living in that prescribed area.

In Nagoya, the 475.7 km of streets and 309 intersections, where more than 1,000 cars pass from 7 a.m. to 7 p.m. each day, were divided into 476 units of 1 km each; a serial number was given to each unit. The residential area was divided by a distance of 25 or 50 m from the street or intersection, as shown in text-figure 2. We counted the number of houses along each street or around each intersection from the residential map of Nagoya that is published every other year. The population for each subarea, i.e., 0–25, 25–50, 50–75, and 75–100 m from the street or intersection was estimated from the 1970



Text-figure 2.—Residential areas around roads and intersections.

Census. From 1969 to 1972, the 780 deaths from lung cancer were plotted on a map of subareas along 207 randomly selected units of the streets and around the 309 intersections. Text-figure 3 presents an example of distribution of deaths from lung cancer within 100 from the streets and intersections. Crude death rate in the areas 25 or 50 m distant was estimated because it is difficult to obtain the exact age composition of the population in each area.

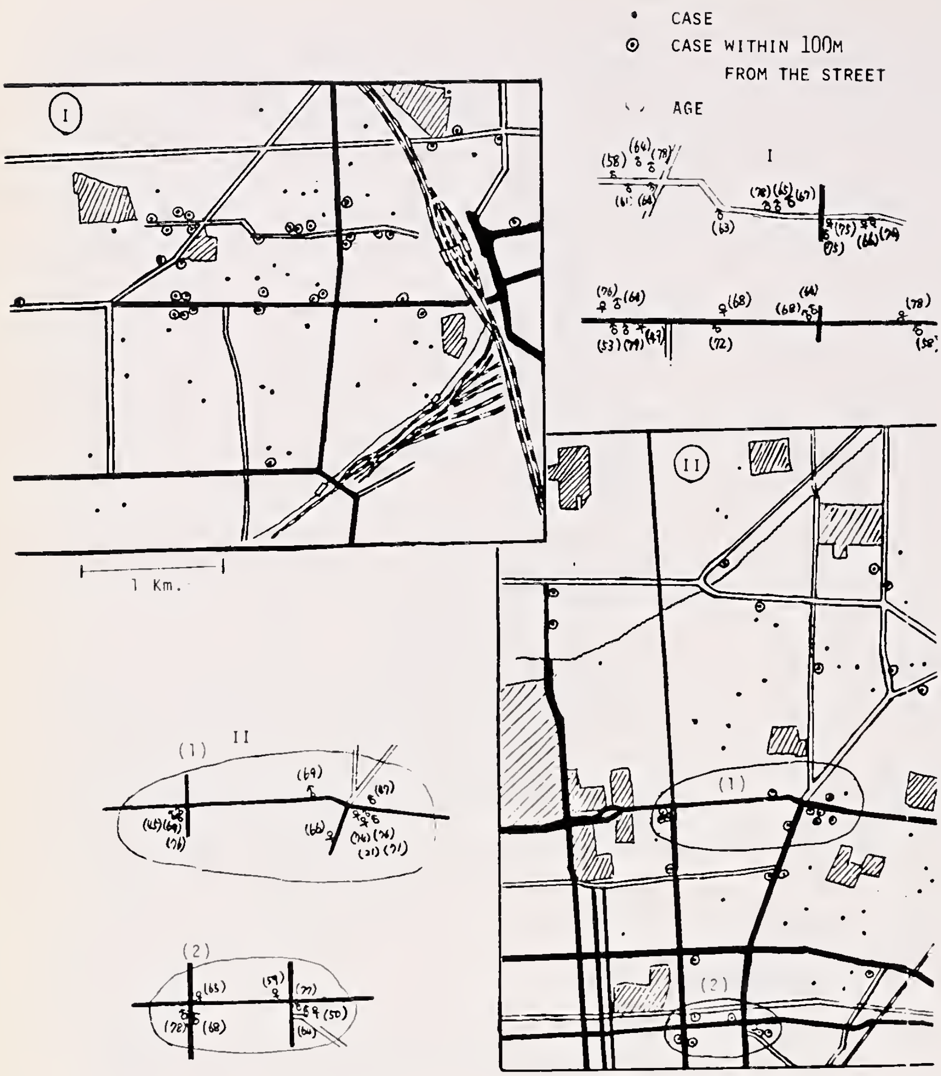
Mortality rate of lung cancer in the areas along the coast of Japan Islands.—The SMR of lung cancer for persons who were more than 40 years old and living in cities and guns was computed for the two periods: 1965–67 and 1969–71 (*1*, *5*). A small number of administrative districts had been united with or separated from adjacent districts during that time; thus 562 cities and 521 guns were examined in 1965–67 and 614 cities and 514 guns in 1969–71 (*6*).

Geographic distribution of SMR of lung cancer was examined in terms of population density, level of education, number receiving welfare assistance, and the presence of chemical or manufacturing industries. Its association with geologic features, meteorologic conditions, and ocean current also was determined (Ministry of Construction, Geographic Survey Institute: Unpublished data).

RESULTS

Association Between Incidence of Lung Cancer Among the Residents Along a Heavily Traveled Street or Intersection and Traffic Volume

The crude death rate for lung cancer in the city of Nagoya was 9.4/100,000 population for both sexes, 13.0 for males, and 5.6 for females. Table 2 shows that this crude death rate for residents living within 50 m of a street and intersection was 14.1/100,000 for both sexes, 20.2 for males, and 8.1 for females, whereas the values for those within 50 m of an intersection were 14.0, 21.8, and 6.2, respectively. These figures were slightly higher than those for the whole city, although the difference was not significant. The rate for the residents whose houses front on the street and who were thus exposed to auto exhaust more intensively than those living further away was similar to that for the whole city. The death rate for lung cancer for residents along the street was examined according to traffic volume (table 3). The rate was higher for the residents of the area where daily more than 20,000 cars traveled than those of the area with 1,000–20,000 cars.



TEXT-FIGURE 3.—Distribution of deaths from lung cancer within 100 m of intersections.

TABLE 2.—*Crude death rates of lung cancer among residents by distance from the intersection or street, Nagoya, 1969–72*

Category	Estimated population	Deaths, 1969–72			Rate/100,000/yr		
		Total	Male	Female	Combined	Male	Female
All residents	203.6 million	763	538	225	9.4	13.0	5.6
Residents within 50 m of intersection	24,752	14	10	4	14.1	20.2	8.1
Residents within 50 m of street	176,723	99	77	22	14.0	21.8	6.2
Residents whose houses front on the street	115,178	48	38	10	10.4	16.5	4.3

TABLE 3.—*Crude death rates of lung cancer among residents by distance from the street and traffic volume, Nagoya, 1969–72*

Traffic volume	Distance, m	Estimated population	Deaths, 1969–72			Rate/100,000/yr		
			Total	Male	Female	Combined	Male	Female
More than 20,000 cars/12 hr/day	0–50	89,464	62	49	13	17.3	27.4	7.3
	50–100	139,407	67	44	23	12.0	15.7	8.2
1,000–20,000 cars/12 hr/day	0–50	87,259	37	28	9	10.6	16.0	5.2
	50–100	96,965	37	20	17	9.5	10.3	8.8

The residents living within 50 m of the street had a higher death rate than those within 50–100 m, although the difference was not significant; the rates are approximately the same, particularly for women.

Table 4 presents the results of observations of residents around an intersection. The rate was higher for the residents in the area of 25–75 m from the intersection than for those within 25 m. The death rate for lung cancer among residents whose homes front on the street was computed in relation to traffic volume. A slight upward gradient is shown with increasing traffic volume for both sexes, but no significant difference was observed (table 5). The average age at death from lung cancer for male residents was 65.3 years in an area with more than 30,000 cars/day and 63.0 in those with 1,000–9,999 cars; that for corresponding female residents was 68.8 and 66.0, respectively. Thus people with intensive exposure to gas exhaust and dust died from lung cancer at an older age than those who inhaled less polluted air. This finding is inconsistent with our working hypothesis.

SMR of Lung Cancer in the Coastal Areas

The specific death rate due to lung cancer of persons more than 40 years of age in Japan in 1965–67 was 27.7/100,000 for both sexes, 42.6 for males, and 15.0 for females; in 1969–71, it was 30.9, 48.1, and 16.1, respectively.

In metropolitan areas with populations of more than 1 million, such as Tokyo, Osaka, and Yokohama, the SMR for lung cancer was less than 120 for both periods, although it was more than 140 for males in 55 of 516 cities (10.7%) and 60 of 465 guns (12.9%) in 1965–67, and 64 of 614 cities (10.4%) and 60 of 514 guns (11.7%) in 1969–71. (The rate in some cities and guns for 1965–67 could not be calculated because of unification or separation of administrative areas.) Thirty (54.5%) of these 55 cities and 28 (46.7%) of the 60 guns, and 36 (56.3%) of the 64 cities and 36 (60%) of the 60 guns (1969–71) (rates calculated for males) are located along the Pacific coast or the Sea of Japan. In 1969–71, 43 (65.2%) of the 66 cities and 24 (42.9%) of the 56 guns with an SMR of 120 to 139 faced the sea.

No significant correlation of geographic distribution between the SMR of lung cancer by city and gun and various socioeconomic conditions in each district (such as population density, proportion of elderly or aged in the population, level of education, business conditions, number receiving welfare aid, and location of chemical and other modern industries) was observed. The SMR for lung cancer by city and gun was not associated with the geographic distribution of rivers, Japanese geologic features, or ocean currents around the Japanese Islands. Furthermore, the SMR did not correlate with meteorologic conditions of atmospheric temperature and rainfall.

Almost all cities and guns with a high SMR for lung cancer show a low SMR for stomach cancer, although the difference of SMR for cancer at all sites was slight.

TABLE 4.—*Crude death rates of lung cancer among residents by distance from intersection and traffic volume, Nagoya, 1969–72*

Traffic volume [a]	Distance, m			
	0–25	25–50	50–75	75–100
30,000 or more	8.4	16.6	19.1	7.7
20,000–30,000	9.7	19.4	17.2	7.6
Less than 20,000	—	19.4	4.8	9.5

[a] Volume indicated is for a 12-hr day.

DISCUSSION

The incidence of lung cancer is affected by the proportion of aged people in the population, migration rate, duration of residence, and topographic condition of the area, in addition to cigarette smoking and occupational exposure to carcinogenic substances. Auto exhaust is considered a causal agent. This study was limited to the examination of the relationship between lung cancer and traffic volume (which is proportional

TABLE 5.—*Crude mortality rates of lung cancer among residents whose houses front on the street by traffic volume*

Traffic volume	Estimated population	Deaths, 4-yr period			Rate/100,000/yr			Average age at death			
		Total	Male	Female	Combined	Male	Female	Male	Average no. deaths/yr	Female	Average no. deaths/yr
30,000 or more	24,856	16	12	4	16.1	24.1	8.0	65.3	9.0	68.8	5.7
20,000–29,999	28,885	15	12	3	13.0	20.7	5.2	58.4	15.1	67.0	8.2
10,000–19,999	34,827	13	11	2	9.3	15.8	2.9	64.3	6.5	68.0	2.8
1,000–9,999	26,611	4	3	1	3.8	5.6	1.9	63.0	5.0	66.0	—
Total	115,178	48	38	10	10.4	16.5	4.3	62.6	10.1	67.8	5.3

to the concentration of exhaust), although the effect of the fumes is influenced by many factors already mentioned.

The crude death rate is higher among male residents who had lung cancer and lived within 50 m of a street or intersection with a traffic volume of more than 20,000 cars a day than among those who lived at a location with fewer cars passing through the area.

No difference was observed between the 2 female groups. Among the residents living near the intersections where we detected high concentrations of exhaust, the mortality was higher for those in areas 25–75 m from the intersection than for those within 25 m. This is inconsistent with our working hypothesis, but we must point out that fewer people live within the 25-m radius. The number of deaths from lung cancer among the residents whose houses front on the street was unexpectedly low, but for both sexes, a slight upward gradient of the rate was observed with increasing traffic volume. The average age at death is slightly higher among those who live in an area with a traffic volume of more than 30,000 passing cars than those living on streets with less than 10,000.

The above results do not give consistent evidence for the association between traffic volume and incidence of lung cancer, although they are suggestive. Traffic jams in Nagoya started 15 years ago; perhaps this is too short a period to accumulate sufficient and definitive data on the incidence of lung cancer. Accumulation of more data will allow us to compute age-adjusted mortality rates and will provide us with more direct evidence of this association.

The epidemiologic method used in this study may be applicable for investigating other health hazards occurring in limited areas along our streets and highways.

The study of the geographic distribution of lung cancer in small areas is only preliminary. Most cities along the coast have various factories, the waste products of which infiltrate the air and water supplies and thereby expose the residents to hazardous industrial chemicals. More recently, such industrial plants have been established in rural areas. However, industrial pollution in these areas is less severe than in metropolitan ones.

The problem with these data is that the population in the rural areas and some cities is small; also, the mortality rates from lung cancer may not be stable from year to year. Almost all cities and guns with a high SMR of lung cancer have a low one of stomach cancer, although in a comparison with SMR of cancer at all sites, the difference is slight.

A high incidence of lung cancer was observed among Japanese residents of many small islands that have no air pollution. Doll et al. (*7*) reported that the highest incidence of lung cancer is in native Hawaiians in Hawaii and Maoris in New Zealand, who are 2 representative groups living in countries with little or no heavy industrial pollution.

If incidence of lung cancer is high among people along the coast as our findings suggest, further study of some associated factors, including ozone and atmospheric air with salts that may predispose to lung cancer, is essential.

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Epidemiology of Leukemia and Aplastic Anemia[1,2]

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ABSTRACT—Age-adjusted mortality rates of all blood-related diseases [International Classification of Diseases (ICD) No. 280–289 and 205–209] were stable in Japan from 1955 to 1973. Age-specific mortality rates decreased in the younger and increased in the older age groups annually. The average increase in lifespan for these diseases was prolonged 5 and 9 years for males and females, respectively, during this time. Age-adjusted mortality rates of all blood-related diseases in many countries showed similar frequency. This contrasted with a marked intercountry difference in mortality from leukemia or aplastic anemia alone. We interpreted these results as signaling that genetic factors played a significant role in the etiology of these blood and hematopoietic diseases and that socioenvironmental factors may have influenced average age at death. Etiologically, fatal blood and hematopoietic diseases, such as leukemia, aplastic anemia, etc., were closely related. The incidence rate of leukemia was high in younger age groups, whereas that of aplastic anemia was high in the older people. The occurrence of leukemia was high in the countries with high living standards, and aplastic anemia was more prevalent in the countries with lower living standards than in the United States and the developed countries of Europe. The occurrence of leukemia was inversely proportional to that of aplastic anemia in 10 countries. We deduced from the data reviewed that environmental factors influenced the incidence of leukemia and aplastic anemia, which represent 85% of all blood-related diseases.—Natl Cancer Inst Monogr 47: 23–30, 1977.

The mortality curve of leukemia relating age and sex exhibits a different pattern from that of solid malignant neoplasms but a similar one to that of blood and hematopoietic diseases. The curve is characterized by a gradual decrease from birth to the age of 10; after 40 years of age, it increases with age again. The group between 15 and 35 years shows a low rate of mortality. Other epidemiologic characteristics of these diseases are similar to each other. We examined their annual trend and distribution and observed that age-adjusted mortality rates of the combined group of diseases of the blood and hematopoietic system, excluding lymphatic leukemia, had been almost stable in Japan from 1955 to 1973. This study analyzes these epidemiologic findings and also examines the relationship between leukemia and aplastic anemia.

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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MATERIALS AND METHODS

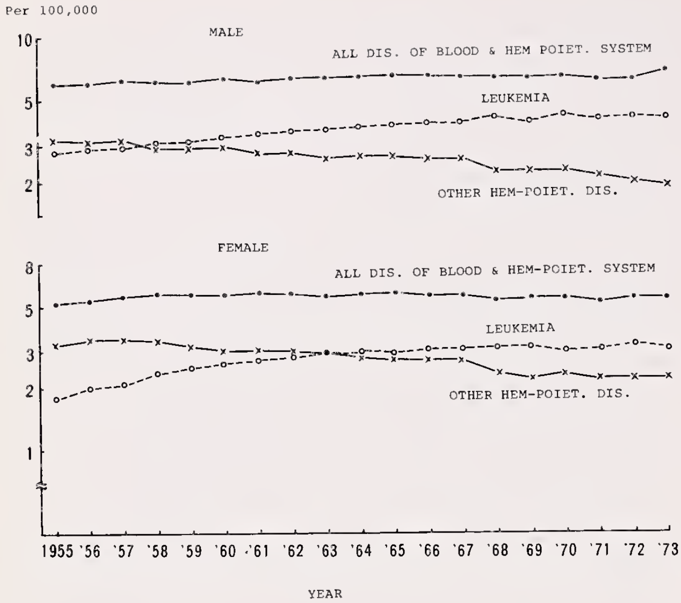
Vital Statistics in Japan (*1*) between 1950 and 1973, World Health Statistics Reports (*2–6*), publications on cancer mortality for selected sites in 24 countries (*7–11*), and several other epidemiologic reports (*12–16*) on blood and hematopoietic diseases were used as bases for our analysis.

Deaths from diseases of the blood and hematopoietic system [International Classification of Diseases (ICD) 290–299, 6th and 7th revision (*17, 18*); 280–289, 8th revision (*19*)], excluding lymphatic leukemia, were selected from all causes of deaths. We designate the above group of diseases (ICD 280–289 and 205–209) as all the blood-related diseases discussed in this paper. Some changes in list number of ICD were made between the 6th and 7th and the 8th revisions. Diseases of the spleen [298.0 (*17, 18*)] were omitted from those of the blood and hematopoietic listing in the 8th revision (*19*), as they accounted for only 3–3.5% of all blood-related diseases. We could not separate these figures from those for the total between 1950 and 1967, as deaths from diseases of the spleen were not noted on the vital statistics. Therefore, the age-adjusted death rate of all blood-related diseases was slightly higher than the actual figures for this period.

Age-adjusted mortality rates for each disease and all blood-related diseases were computed with the use of Segi-Doll's rounded world population (*12*) for 1955–73.

RESULTS

Text-figure 1 shows the annual trends for the age-adjusted mortality rates with respect to all blood-related diseases. The rate was almost stable in Japan from 1955 to 1973 at a level of about 6.0/100,000 and 5.5/100,000 in males and females, respectively. In a comparison of the annual trend of the age-adjusted mortality rate for leukemia with that for other related diseases, we observed a gradual increase in the leukemia group and a gradual decline in the other diseases for both sexes. When leukemia and aplastic anemia were grouped together, the pattern of the mortality curve ran nearly parallel to that for leukemia

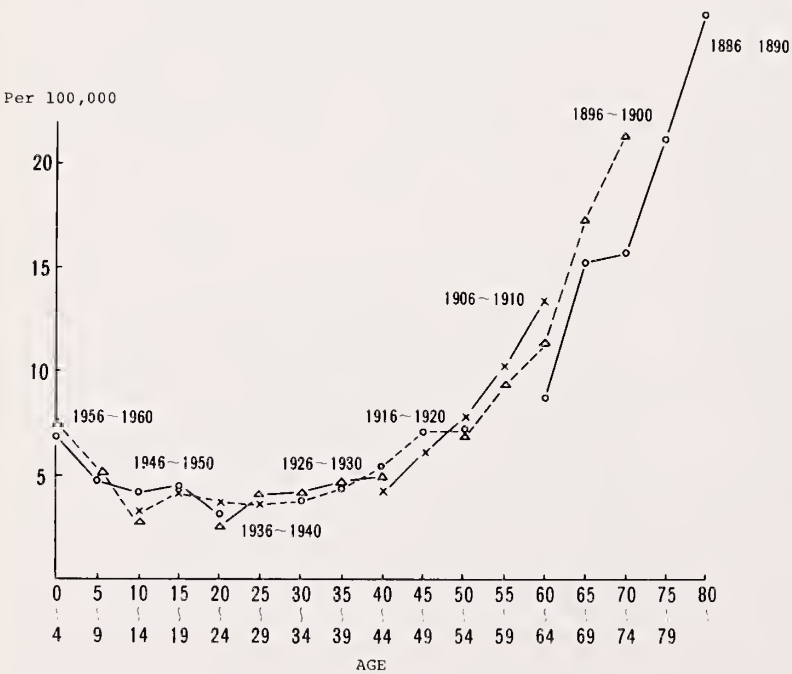


TEXT-FIGURE 1.—Age-adjusted mortality rates of leukemia and blood and hematopoietic diseases and all blood-related diseases in Japan, 1955–73.

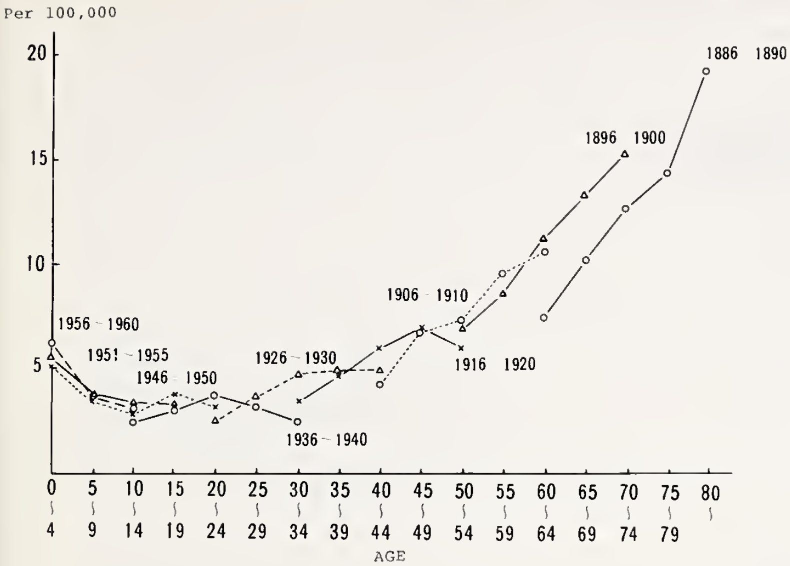
alone. However, the curve for leukemia alone began to show signs of stabilization around 1968; the mortality rates of leukemia by type, such as acute myeloid, chronic myeloid, and other acute and chronic forms (except lymphatic), were stable between 1968 and 1973.

From the examination of the above trend for contemporary birth cohorts, the age-specific mortality rate attributable to all blood-related diseases in males was estimated to have been low in cohorts of those born between 1886 and 1890 and to have risen until the 1916–20 cohort, when it became virtually stable. A similar trend was observed in females, but it began to level off in the cohort born in or around the year 1906 (text-figs. 2, 3).

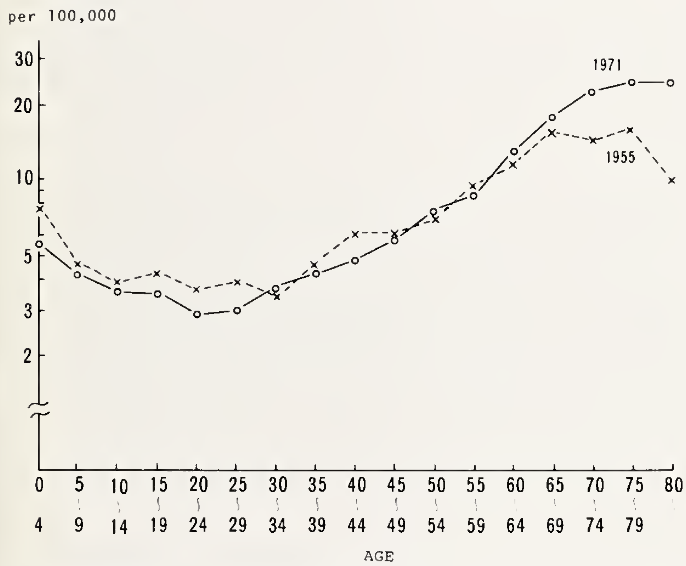
We compared age-specific mortality rates of all blood-related diseases by sex for 1955 and 1971, since the age-adjusted mortality rates for these years were the same. Text-figure 4 shows that the rate for males up to 35 years old was slightly lower in 1971 than in 1955, whereas for those between 45 and 60 years, the rates in both years were approximately the same. In contrast, for those over 65, the rate was considerably higher in 1971 than in 1955. For females, the rates in both years were approximately the same until the age of 9. Between 10 and 54 years, it was lower in 1971 than in 1959, whereas in elderly women (i.e., those aged 60 and over), it was higher in 1971 than in 1955; that is, the death rate has been declining in younger ages and increasing in the elderly for these periods (text-fig. 5). Between 1955 and 1973, the average age at death rose from 37.3 to 43.2 years for males and from 34.0 to 45.2 for females.



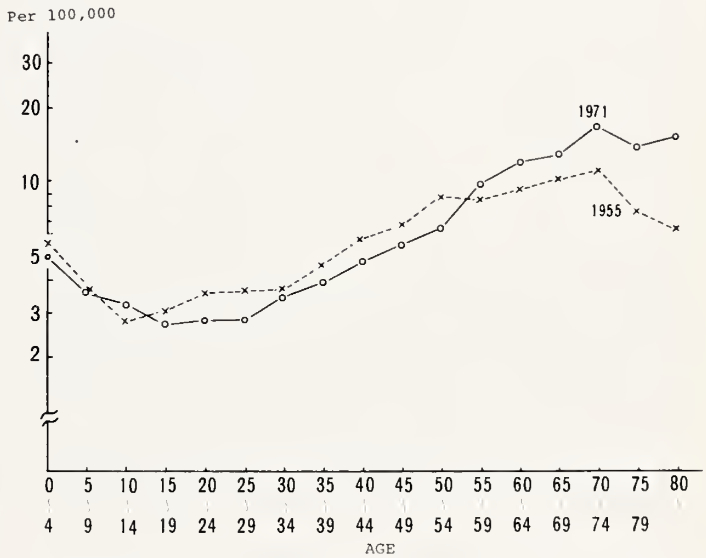
TEXT-FIGURE 2.—Mortality rates of all blood-related diseases by birth cohort in Japanese men.



Text-figure 3.—Mortality rates of all blood-related diseases by birth cohort in Japanese women.



Text-figure 4.—Age-specific death rates of all blood-related diseases in Japanese men, 1955 and 1971.



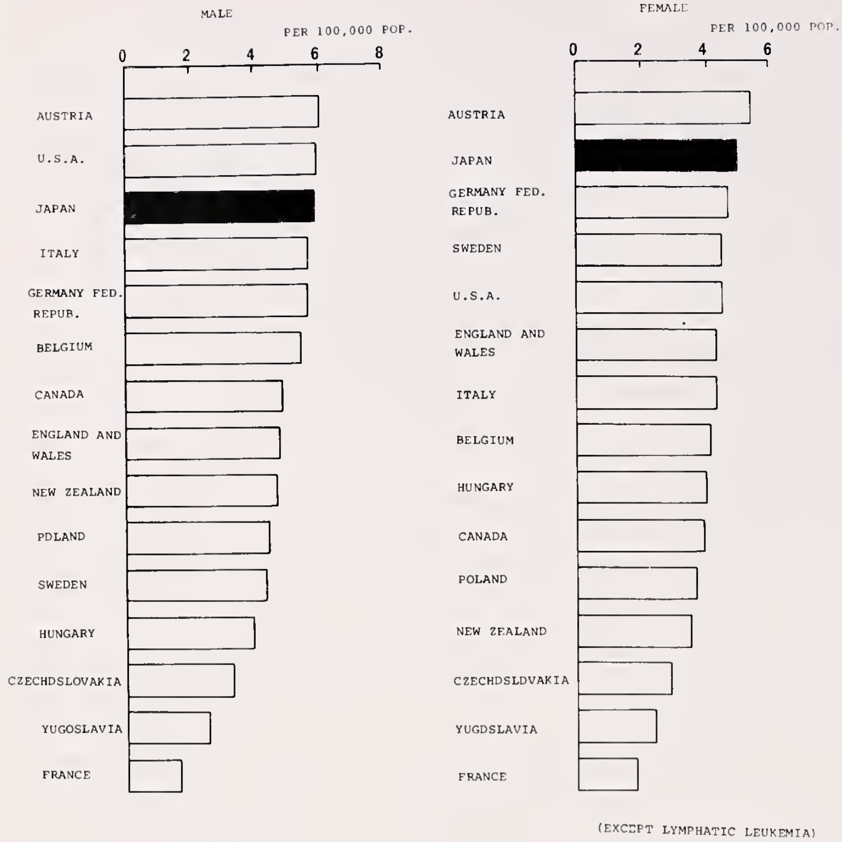
Text-figure 5.—Age-specific death rates of all blood-related diseases in Japanese women, 1955 and 1971.

Between 1955 and 1971, 92,391 deaths were due to all blood-related diseases. The sex ratio was nearly 1.0 (computed at 1.03), although it was 1.26 in leukemia only, 0.86 in the aplastic anemia group, and 0.79 in the other blood and hematopoietic diseases.

Age-adjusted mortality rates of all blood-related diseases in 15 countries of the world were similar, although France and Yugoslavia showed low rates (text-fig. 6). However, marked differences became apparent among the various countries when the age-adjusted mortality rates for leukemia or aplastic anemia were examined separately from other related diseases.

In the age group less than 40 years, leukemia accounted for about 70% of the deaths from all blood-related diseases. In the group 40 years old and over, in contrast, the deaths from leukemia decreased gradually and those from aplastic anemia increased correspondingly with advancing age.

In Japan, age and sex distribution and the clinical picture of unspecified anemia (ICD 285.9) are similar to those of aplastic anemia. When laboratory examinations are incomplete and improperly performed, it is difficult for the physician to diagnose aplastic anemia correctly. We arbitrarily included unspecified anemia with

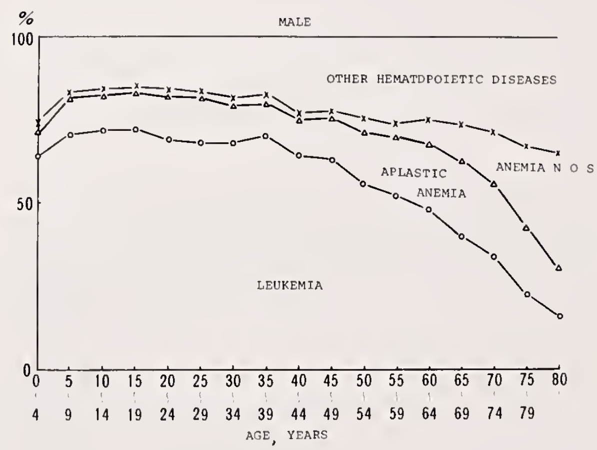


TEXT-FIGURE 6.—Age-adjusted mortality rates of all blood-related diseases in the countries of the world, 1970 (Segi-Doll's rounded world population).

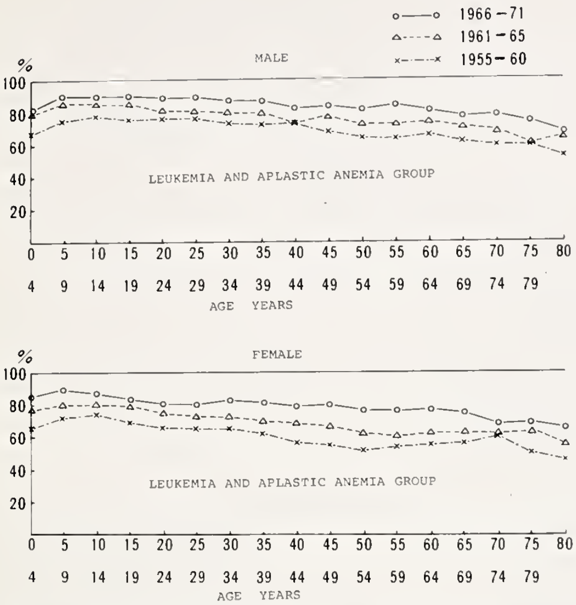
aplastic anemia, though these two diseases might be different etiologically. Mortality trends between 1955 and 1971 and age and sex distribution of the aplastic anemia group were about the same as those of aplastic anemia alone.

Text-figure 7 presents an analysis, by age and sex, of the 92,391 deaths due to all blood-related diseases. The percentages of deaths by age attributable to each type of disease when the total number of deaths in each age group is taken as 100% are shown. Among males, leukemia accounted for about 70% of the deaths occurring up to the age of 39 years. The percentage dropped rapidly thereafter to a level of approximately 20% at the age of 75–80 years. The mortality from the aplastic anemia group showed little change between the age of 5 and 44 years but then gradually increased. Similar trends were observed for females, although the percentage of each disease was somewhat lower than that for males.

In text-figure 8, the 17 years of observation have been divided into three periods (1955–60, 1961–65, and 1966–71), and the combined proportion of the two disease categories "leukemia plus aplastic anemia group" in all blood-related diseases was plotted for each age. The three periods showed fairly similar age distribution; their percentages consistently increased since the 1955–60 period. These facts support the impression that these two disease categories have the same origin fundamentally.



TEXT-FIGURE 7.—Percentages of deaths from leukemia, aplastic anemia, anemia not otherwise specified (NOS), and other hematopoietic diseases by age in all blood-related diseases in Japan, 1955–71.



TEXT-FIGURE 8.—Percentages of deaths from leukemia and the aplastic anemia group in all blood-related diseases in Japan.

The percentages of deaths from leukemia and the aplastic anemia group in those from all blood-related diseases in Japan and nine other countries is indicated in text-figure 9. These two disease categories (leukemia and aplastic anemia) were responsible for approximately 85% of the deaths. In countries such as the United States and Denmark, the prevalence of leukemia was high and that of aplastic anemia was low, whereas in Japan and Ireland, the reverse was true. Nonwhites in the United States also showed a considerably lower prevalence of leukemia, but this was offset by the high mortality from hemolytic anemia. In the 10 countries listed in text-figure 10, the percentages of deaths from leukemia and aplastic anemia were inversely correlated.

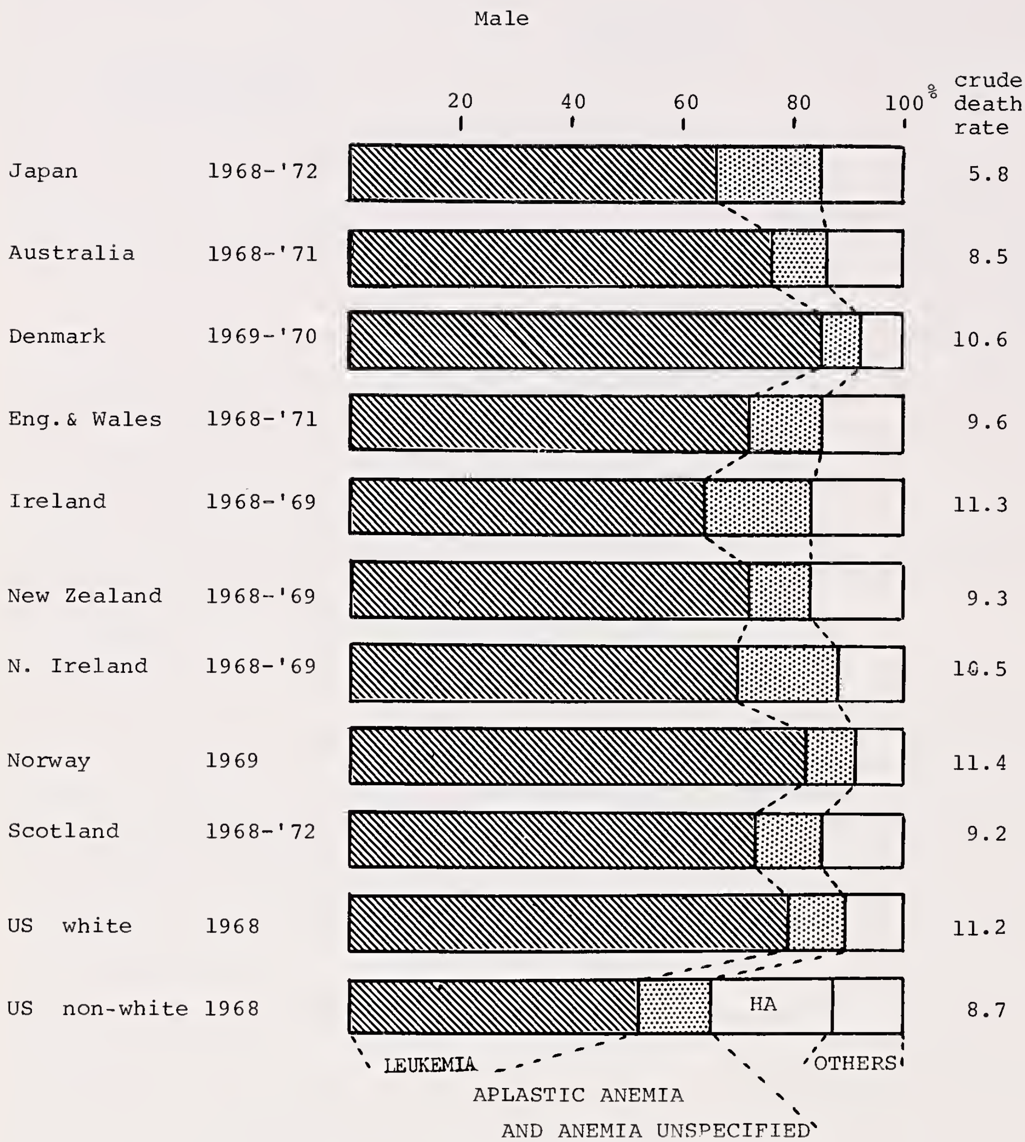
DISCUSSION

Following World War II, the mortality rate for all blood-related diseases increased and was inversely correlated to the decrease of deaths due to infectious diseases in Japan. This may be explained only by the prevalent use of powerful antibiotics and the improvement of socioeconomic and public health conditions. Later, as the mortality rate from infectious diseases ceased to decrease, the mortality rate of all blood-related diseases stabilized.

From 1955 to 1973, numerous changes occurred in the mortality patterns in Japan. Explosive industrialization led to more alterations in environmental pollution. The fact that mortality from all blood-related diseases remained almost constant throughout this 19-year period suggests that changing socioenvironmental conditions had little influence on the deaths from these diseases. Moreover, the role played by other factors could conceivably be only a minor one. Such factors include exposure to ionizing radiation at low levels as observed among X-ray technicians for the last decade *(20)* and the effects of certain drugs.

Children who died from aplastic anemia or leukemia may have had some inherent deficiency in their bone marrow. In line with this hypothesis, the findings of this study indicated that persons afflicted with this predisposition, whether or not they survive until adulthood, die at a certain fixed rate. The age distribution of the death rate can be fitted with three kinds of regression curves: the death curve for childhood, for age 45 and older, and, lastly, the one for ages 20–45. All these regression curves are fitted to normal distribution. The death curves for those aged 45 and older have been shifting to the right annually and are approaching that of the general population. Between 1955 and 1973, the average lifespan was prolonged about 5 and 9 years for males and females, respectively. Consequently, it would appear that those highly susceptible to bone marrow diseases die shortly after birth or during early childhood from blood-related diseases or infections, whereas the remainder succumb gradually as they become older. The lifespan of these people depends on their capacity to resist infections, their environment, and the extent to which they become exposed to noxious agents. However, the progress of medical care and the improvement of living standards and sanitation prolong the age at onset of the disease among persons susceptible to such blood and hematopoietic diseases. The small intercountry difference of age-adjusted mortality rates of all blood-related diseases might be interpreted as suggesting that each country or each race has approximately the same proportion of individuals highly susceptible to bone marrow disease in a contemporary birth cohort.

The trend and age and sex distribution of leukemia, aplastic anemia, and the related diseases suggest that these conditions are closely akin to one another, and that genetic factors are probably

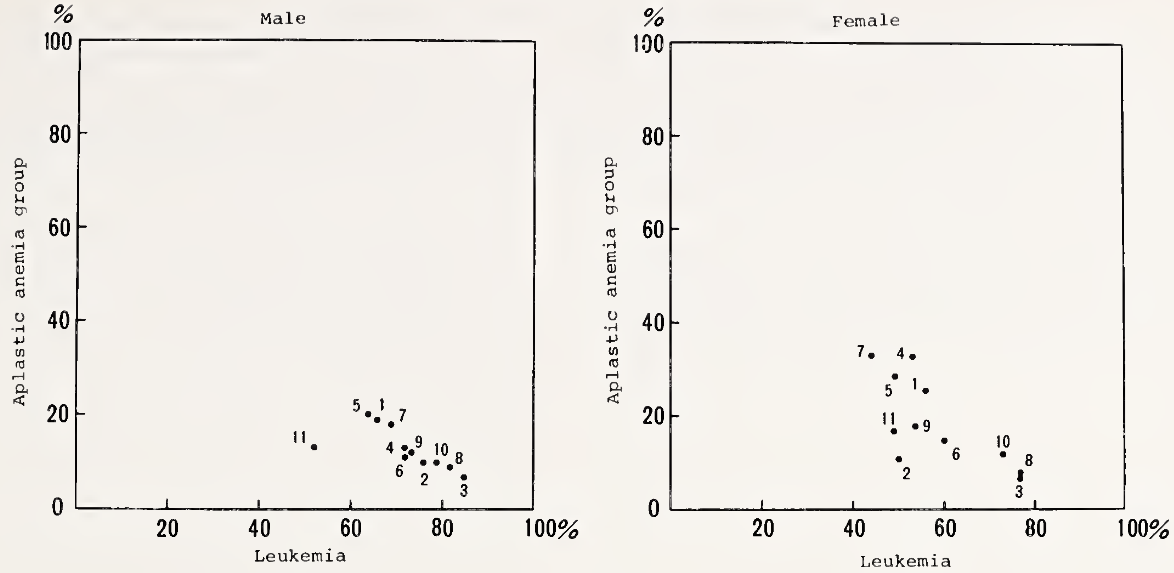


TEXT-FIGURE 9.—Percentages of deaths from leukemia, the aplastic anemia group and others in all blood-related diseases. HA = hemolytic anemia.

significant in their etiology. Clinical findings provide some examples that show a certain type of aplastic anemia considered a preleukemic condition and that many cases of aplastic anemia develop into acute leukemia (*21–27*).

The proportion of leukemia, aplastic anemia, and others to all blood-related diseases in many countries of the world suggests that each country may have its own specific ratios of these diseases. The occurrence of leukemia was inversely proportional to that of aplastic anemia in 10 countries. Leukemia occurs proportionately in the countries with high living standards, and aplastic anemia is relatively prevalent in the countries with lower living standards than those of the United States and developed European countries. Further studies should be conducted to learn why more individuals develop leukemia than aplastic anemia and vice versa and why age and sex distributions of these diseases are different among countries.

Our studies were based on fatal cases, not on those who are cured, convalescent, or morbid. These groups may have different features and be affected much more by environmental conditions.



1: JAPAN 2: AUSTRALIA 3: DENMARK 4: ENGLAND-WALES
5: IRELAND 6: NEW ZEALAND 7: NORTHERN IRELAND 8: NORWAY
9: SCOTLAND 10: US (WHITE) 11: US (NON-WHITE)

TEXT-FIGURE 10.—Correlation between percentages of deaths from leukemia and the aplastic anemia group in all blood-related diseases, 1972 (all blood-related diseases = 100%).

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Cancer Study on a Cohort of Atomic Bomb Survivors [1]

Hiroo Kato, ***M.D.*** [2]

ABSTRACT—Since 1950, the Radiation Effects Research Foundation (formerly Atomic Bomb Casualty Commission) in Hiroshima and Nagasaki, Japan, conducted a large-scale study on a cohort of 109,000 persons to determine the late effects of atomic bomb (A-bomb) radiation. A brief review was made on carcinogenesis in this cohort. The risk of leukemia decreased since the peak incidence years of 1950 to 1954 but continued to be higher in the heavily exposed group than in the controls even as recently as 1970 to 1972. This decreasing trend differed according to age at the time of bombing. The risk of cancer, excluding leukemia, increased from about 1960 to 1965 in the group exposed to 100 rads or more after a latent period of 15 to 20 years. The susceptibility to radiation-induced cancer differed by organ, and a definite association with A-bomb radiation for thyroid, lung, and breast cancers, and a possible relation for salivary gland and stomach cancers was found. Carcinogenic factors such as smoking, hormonal conditions, and so on, but not radiation, also were investigated; the interaction between radiation and other carcinogenic factors was not apparent. Ongoing research on immune response should provide clues for study of the mechanism of radiation carcinogenesis.—Natl Cancer Inst Monogr 47: 31–32, 1977.

Besides the well-known delayed effect of atomic bomb (A-bomb) irradiation on the development of leukemia, the incidence of cancers other than leukemia has also increased recently among A-bomb survivors, who not only have been exposed to possible carcinogenic effects of A-bomb radiation but also to various carcinogens present in the external and internal environments. Therefore, it is important to investigate other factors related to the occurrence of cancer among A-bomb survivors. Since 1950, the Radiation Effects Research Foundation [formerly Atomic Bomb Casualty Commission (ABCC)] has conducted a large-scale group study to investigate any delayed effects of A-bomb radiation, a discussion of which follows.

MATERIALS AND METHODS

The first set of data came from investigations of the mortality of a fixed population (109,000 persons) and the pathology study of those among this population whose bodies were autopsied. The mortality study checked the records of deaths by the Koseki (family registration system) records. In the pathology study, autopsies were performed at the high rate of 30 to 40%; thus they were unbiased as to cause of death, sex, age, or exposure status.

Since 1958, biennial, complete physical examinations were performed on a subsample of 20,000 individuals. The second set of data concerned the study of 2,600 A-bomb survivors exposed in utero and the cohort-type genetic study of 54,000 children born to A-bomb survivors. Individual exposure dose estimates were calculated according to exposure distance and shielding for each individual in these fixed populations. Besides death certificates and autopsy and medical records obtained from the biennial physical examinations, the tumor registries in Hiroshima and Nagasaki were major sources for determination of cancer incidence.

Other data such as socioeconomic conditions, occupation, diet, and smoking were obtained from census information, interviews, or mailed questionnaires. This information concerning individuals of the cohort was assembled by record linkage system and was filed on a computer tape by individual six-digit identification numbers.

A citywide tumor registry maintained by their respective city medical associations was in operation since 1957 in Hiroshima and Nagasaki. Technical and financial aid were provided by the ABCC. In the Nagasaki Tumor Registry, the death certificate was the only source of information for about 20% of the registered cases. In Hiroshima, a unique registry of tumors on which histologic examination is made was initiated in 1973 under the auspices of the Prefecture Medical Association in cooperation with pathologists in hospitals and medical schools. Financial support was provided by the National Cancer Institute of the United States. The tissue or specimen was registered at the tissue registry with the histologic diagnosis, according to the Systematized Nomenclature of Pathology code. Reporting of tumor cases by histologic examination was almost complete at this tissue registry. This tissue data bank can be used in pathologic studies whenever nec-

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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essary in the future. In Nagasaki, the same kind of tissue registry was established in 1975.

RESULTS

The increased incidence of leukemia was one of the delayed effects of A-bomb radiation. The risk of leukemia decreased since the peak incidence in 1950 to 1954 but continued to be higher than in controls for the heavily exposed group even as recently as 1970 to 1972.

This decreasing trend differed according to age at time of bombing (ATB). For the ATB group, 0–9 years, the incidence of leukemia increased dramatically from 1950 to 1954 but leveled off around 1960. For the ATB group aged 50+, the increase of incidence began later and continued. The 10- to 49-year-old ATB group showed an intermediate tendency.

The risk of cancer, excluding leukemia, increased from about 1960 to 1965 in the heavily exposed group (100 rads or more) after a latent period of 15 to 20 years. The relative risk of cancer, excluding leukemia, increased in the younger age group, particularly in children less than 10 years old ATB.

The susceptibility of different organs to radiation-induced cancer differed. An association with A-bomb radiation was found for leukemia, and for cancer of the thyroid, lung, breast, and salivary gland. The stomach was the most common cancer site in Japan, and recent analysis revealed an increased mortality rate in the high-dose group, i.e., 300+ rads. Further study is necessary in this area.

The frequency of clinically diagnosed thyroid cancer and nonclinically diagnosed small occult cancers was higher in the heavily exposed group than in the controls.

The risk of lung cancer increased since 1960 in the high-dose, older-aged ATB group. For the younger people in this same group, i.e., those under age 35, the radiation effect had not yet appeared, since this group had not reached the cancer age for this site.

Examination by histologic type showed a tendency for increased risk of almost all types of lung cancer. The small-cell anaplastic type of lung cancer, which is the type least related to smoking, demonstrated the strongest relation to radiation dose.

Although analysis of the relationship between radiation dose and lung cancer by smokers and nonsmokers was inconclusive, the addition of smoking effects to those of radiation resulted in a further increase of relative risk; no interaction between the two factors was apparent. Similar observations were made for occupation and lung cancer. A study of the relationship between breast cancer and such factors as number of pregnancies and age at first delivery also revealed that these factors and radiation additively affected the incidence of breast cancer among heavily exposed women.

Many reports have described the reduced immune response following radiation exposure in animal experiments. Studies of children exposed in utero showed temporary suppression of influenza antibody production. Determinations of hepatitis-B antigen and Epstein-Barr virus antibody titers recently were made for A-bomb survivors, but preliminary analysis showed no apparent relation to exposure dose. However, the preliminary analysis suggested that the proportion of T-cells of the lymphocytes in the peripheral blood decreased in the heavily exposed (200+ rads) group. As expected, the proportion also decreased in cancer patients. The proportion of phytohemagglutinin-responsive lymphocytes also declined in the heavily exposed group and in cancer patients.

These preliminary findings suggest that the immune response in the heavily exposed group may be suppressed. A follow-up of this group is planned with respect to the future possible occurrence of cancer.

The mechanism of radiation-induced cancer has not been well explained. It may be a direct effect of radiation on the cell, but it is also possible that radiation activates "dormant cancer viruses" or suppresses antiviral defense or immune response. We hope that this kind of approach will be helpful in studies of radiation carcinogenesis.

An international cooperative study, NI-HON-SAN, for cardiovascular disease on Japanese living in Japan, Hawaii, and San Francisco has been conducted since 1965. Our cohort in Hiroshima and Nagasaki forms the sample in Japan for this cooperative study. Many characteristics of the population including diet and smoking have been analyzed in relation to the incidence of cardiovascular diseases. It is hoped that a similar kind of cancer study will be performed in the future.

Cancer Registries in Australia[1]

Joyce M. Ford[2]

ABSTRACT—Cancer registries are at an early stage of development in Australia. Population-based registries are located in New South Wales and Western Australia, and of these, only the New South Wales Registry is fully functioning. A hospital-based registry is maintained in Victoria. We have a national cancer registry in principle but it will not be functional for many years. Preliminary statistics for New South Wales indicate a cancer pattern similar to Caucasian populations. Some epidemiologic surveys have been undertaken.—Natl Cancer Inst Monogr 47: 33–35, 1977.

The estimated population (1972) for Australia is 13,132,000. The official figure for aborigines is 106,288. Asians and Africans make up no more than 1.8% of the total; thus most of the people are of European extraction. The median age of urban dwellers is 27.5 years, 86% of whom live in urban areas.

Life expectancy and infant mortality do not compare favorably with those of other developed countries, but the incidence of death from communicable disease is low. Accidents are the major cause of death among the young, and degenerative diseases and diseases of the circulatory system account for half the deaths among middle-aged and elderly persons; cancer accounts for one-seventh.

All seven Australian states have agreed in principle to contribute to national cancer statistics and will collect and categorize basic data according to World Health Organization (WHO) recommendations and codes. Statistics will be collated centrally from uniform data submitted by each State from either population-based cancer registries or hospital morbidity records. However, only three registries are now organized sufficiently for progress reports: New South Wales, Victoria, and Western Australia.

NEW SOUTH WALES

The New South Wales Central Cancer Registry was established in 1971 as an independent branch of the Health Commission of New South Wales; the year of first collection of data was 1972. The Registry covers the total population of the state of New South Wales (4,696,040 in 1972) and of the Australian Capital Territory (165,255 in 1972). In New South Wales, 80% of the people were born in Australia and 15% in Europe; in the Capital Territory, 75% were born in Australia and 21% in Europe. The ratio of urban to rural residents is 6:1.

The major data source for the Registry is a statutory notification form for all cancers (excluding skin but including melanoma of the skin), which is completed on a compulsory basis by all hospitals and radiotherapy departments in New South Wales, excluding Commonwealth hospitals, and on a voluntary basis by two Commonwealth Repatriation hospitals in New South Wales and by two public hospitals in the Australian Capital Territory. Ancillary data are obtained from pathology laboratories and death notifications.

Approximately 1,800 forms are received each week; notification is approximately 85% complete. Forms request demographic data, cancer site, histology, degree of spread, and treatment at each notification. Checks for duplications, errors, and consistency are made, and all data are classified according to WHO codes and guidelines. The data are processed and stored by computer on magnetic tape, establishing a permanent record for each cancer case.

The cancer data are collated to produce basic statistical tabulations and epidemiologic patterns for New South Wales and the Australian Capital Territory. The information is also used for patient follow-up and for special studies.

Because the Registry is in an early stage of development, comprehensive statistics are not yet available. However, preliminary data for the year 1972 indicate that the distribution of cancer by site for New South Wales is similar to that for Caucasian populations (tables 1, 2).

The New South Wales Registry is conducting epidemiologic surveys of: 1) bladder cancer to determine whether any occupational exposure might be a causative agent, with a view to possible control legislation; 2) leukemia and lymphoma to determine the significance of contacts among

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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TABLE 1.—*New cases of cancer, 1972* [a,b]

Primary site [c]	Percent of all new cancers	No. of cases	Incidence rate/ 100,000
Total for New South Wales only	100	5,084	217.5
Lung (162)	22	1,128	48.3
Prostate (185)	10	521	22.3
Colon (153)	8	412	17.6
Stomach (151)	7	351	15.0
Rectum (154)	6	291	12.5
Bladder (188)	6	287	12.3
Solid lymphomas (200), (201, 202)	5	237	10.0
Melanoma (172)	5	229	9.8
Pancreas (157)	3	159	7.0

[a] New patients are defined as persons for whom the date of first definitive treatment for cancer was given as 1972 in answer to question 12, Schedule 13A.
[b] The male population in New South Wales in 1972 was 2,336,727.
[c] *Numbers in parentheses* refer to code number of the International Classification of Diseases Adapted (8th ed).

TABLE 2.—*New cases of cancer, 1972* [a,b]

Primary site [c]	Percent of all new cancers	No. of cases	Incidence rate/100,000
Total for New South Wales only	100	5,050	217.2
Breast (174)	27	1,338	57.5
Colon (153)	11	531	22.8
Cervix (inv.) (180)	6	322	13.9
Uterus (182)	6	290	12.5
Melanoma (172)	5	273	11.7
Ovary (183)	5	245	10.5
Lung (162)	5	232	10.0
Rectum (154)	4	214	9.1
Solid lymphomas (200), (201, 202)	4	211	9.0
Stomach (151)	4	201	9.0

[a] *See* footnote *a*, table 1.
[b] The female population in New South Wales in 1972 was 2,324,828.
[c] *See* footnote *c*, table 1.

patients with these types of cancer, so as to confirm or refute claims made for their horizontal spread; 3) lung cancer in a cohort of Wittenoom Gorge asbestos miners; 4) breast cancer to assess the effectiveness of routine mammography as a screening procedure by determining the false negative rate among Medicheck patients; and 5) cervical cancer to assess present screening procedures and plan the future direction of screening by cervical smear technique in New South Wales.

CENTRAL CANCER REGISTER, MELBOURNE

The Central Cancer Register of Melbourne, established in 1940 but suspended during World War II, is conducted by the Anti-Cancer Council of Victoria within the Ministry of Health. Data are collected from 10 public hospitals for some cancer patients by part-time medical officers employed by the Anti-Cancer Council. The Register has an "end results" and "treatment intention" orientation.

Data, recorded on punched cards, include hospital, age, sex, diagnosis, laterality, stage, mode of onset, time lag to registration, reason for nontreatment, previous treatment (if any), and reason for further treatment. Additional information concerns description of primary (e.g., "in situ," "circumscribed," "extensive," etc.) involvement of lymph nodes, location of metastases, investigation (autopsy, biopsy, cytology, etc.), histology ("anaplastic," "moderately differentiated," "well differentiated," "indeterminate"), treatment intention, treatment technique, technical detail, and follow-up (years of survival). Follow-up is a major function and after 5 years, contact usually has been maintained with 98% of the cases. Data processing will be transferred to computers in the near future.

Information can be supplied to qualified inquirers on written request, more readily if limited to data collected and keypunched. Those associated with the Register have made considerable use of the information in preparing scientific papers and lectures. In addition to four formal reports, the last of which was published in 1964, the number of cases registered, tabulated by sex, cancer site, and age is published.

It has been decided to expand the present Register to cover the total population of Victoria with the assistance of the remaining public and private hospitals. The Register has already taken action to secure the cooperation of private hospitals and pathologists in private practice. Funding for the extra workload may be from Government sources.

WESTERN AUSTRALIA CANCER REGISTER

Western Australia, with an area of just under 1 million square miles, has little more than 1 million inhabitants, 73% of whom were born in Australia and 23% in Europe.

The Western Australia Central Cancer Register, a section of the Epidemiology Division of the Public Health Department of Western Australia, began as a small register in 1958 but did not become functional until 1963, when medical records at the five teaching hospitals were searched

regularly for patients with cancer. In 1971, the Register was reorganized and extended to encompass all hospitals in Western Australia by linking to hospital morbidity those statistics that include patients in all hospitals but not residents of nursing homes.

The Western Australia Central Cancer Register is thus a statewide population-based epidemiologic register, deriving its information from a hospital morbidity survey form that identifies cancer cases at all public and private hospitals. From these data, a cancer abstract card is completed by Register clerks, either at the hospitals or from information received by mail at rural institutions.

Lymphoproliferative and Myeloproliferative Disease in Tasmania[1]

J. Norelle Lickiss,[2] A. G. Baikie,[3] *and* J. Panton[4,5]

ABSTRACT—Tasmania, an island state of the Australian Commonwealth with a population of 400,000 of predominantly Anglo-Saxon heritage, has relatively centralized oncology services. A study was undertaken of all patients known in December 1971 and of all new cases diagnosed since January 1972 with all forms of leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, and other myeloproliferative and lymphoproliferative disorders. Data were obtained with respect to lifetime residential and occupational history, schools attended, and known familial cases of any of the myeloproliferative and lymphoproliferative disorders —Natl Cancer Inst Monogr 47: 37–39, 1977.

The recent burgeoning of interest in lymphoproliferative and myeloproliferative disorders is attributable to many factors: improvements in therapy, increasing knowledge concerning the role of viruses in the etiology of these disorders in animals (*1*), and recognition of transmissibility across species (*2*), sometimes with a change in manifestation. Studies associated with Burkitt's lymphoma demonstrate that host factors can profoundly influence human response to viruses such as the Epstein-Barr (EBV) (*3*). Clarification of human constitutional factors predisposing to these disorders (*4–6*), and conceptual and technical developments in relation to the cells concerned in these disorders (*7, 8*) have contributed to our understanding. Recent controversial reports of possible case-to-case transmission in Hodgkin's disease (*9–16*) and increasing realization of possible links between lymphomas and leukemias in man (*17*) and animals have been considered. Each of these factors gives impetus to epidemiologic studies, preferably closely linked with clinical and laboratory studies. Perspectives have been sharpened by editorial comment in many leading journals (*18–21*); relevant to the present undertaking is the editorial remark that, "Perhaps more than anything we lack a comprehensive detailed long-term area-by-area study of Hodgkin's disease and other lymphomas" (*19*).

Tasmania offers advantages for epidemiologic studies: It is an island state with well-defined geographical boundaries, a relatively stable population of convenient size (approximately 400,000), and a wide variety of socioeconomic situations. The habitats range from isolated rural villages and mining towns to provincial cities (130,000 people live in Hobart, the capital, and 63,000 in Launceston). A wide spectrum of occupations exists, ranging from deep-sea fishing to wood-related industries, mining, agriculture, and lavender farming (*22*). Medical services with regard to myeloproliferative and lymphoproliferative disorders are fairly centralized. Despite the absence of a formal cancer registry, a high level of case notification is made possible by means of a network of interested radiotherapists, pathologists, and other clinicians.

The Tasmanian study is simple in concept; we hope to have the following questions (among others) answered:

1) What is the pattern of distribution, over space and time, of these disorders in Tasmania? Does the pattern vary according to disease entity?
2) Is any space/time clustering apparent with respect to individual diseases or to groups of diseases (e.g., groupings based on cell characterization)?
3) Is any space/time clustering apparent with respect to residential history?
4) What is the experience of defined regions (e.g., census districts) over defined time intervals with respect to prevalence and incidence of these disorders?
5) Do clinical manifestations or cell characterization vary with locality or socioeconomic milieu?
6) What familial patterns are detectable?

The study falls naturally into four phases:

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

[2] Department of Community Health, University of Tasmania, Hobart, Australia.

[3] Department of Medicine, University of Tasmania; deceased 1975.

[4] Department of Community Health, University of Tasmania.

[5] We acknowledge the collaboration of clinicians and pathologists throughout Tasmania, especially the radiotherapists of Peter MacCallum Clinics, Hobart and Launceston. The clerical assistance given by Mrs. L. Johansen, University of Tasmania, is appreciated.

In 1971, informal preliminary studies noted the location at diagnosis of southern Tasmanian cases known since 1958. Two medical students (Boyle M, U'Ren R: Unpublished observations) analyzed available mortality and morbidity data for the whole state for the same period.

An attempt was made (and continues to be made) to locate every living patient who had been diagnosed in December 1971. The pathologic diagnosis in this and in the following phase was accepted as given. The categories used in Tasmania until recently were: acute leukemia (AL), chronic granulocytic leukemia (CGL), chronic lymphocytic leukemia (CLL), Hodgkin's disease (HD), lymphosarcoma (LS), reticulum cell sarcoma (RCS), follicular lymphoma (FL), other lymphomas (OL), myeloma (M), polycythemia vera (PV), and myelofibrosis (MF). Data collection and analysis are not yet complete, but prevalence is noted in table 1. No doubt some cases have not been located, and the figures indicate trends only.

A prospective study of new cases diagnosed from January 1, 1972, to December 31, 1975, has been undertaken. With the help of colleagues throughout Tasmania, we attempted to find every new case in the diagnostic categories indicated above. Case location was difficult in the more distant areas, but a large body of data has been accumulated concerning residential and occupational history, schools attended, and, more recently, familial cases.

In addition, when 2 or more cases of any of these disorders have been located in individuals within the first degree of kinship or in members of the same household, further information is being sought and familial history is being prepared. Apparently, such families are not uncommon; although this aspect of data collection has only recently received emphasis, at least 20 families are known. Anecdotal material was recorded, including some information on domestic animals.

TABLE 1.—*Lymphoproliferative and myeloproliferative disorders in Tasmania*

Diagnosis[a]	Cases known Dec. 1971	New cases 1972	1973	1974	1975 (to Oct.)	Total
AL						
<15 at diagnosis	10	7	7	5	3	22
≥15 at diagnosis	7	11	9	11	9	40
CGL	9	3	5	3	1	12
CLL	36	9	8	9	10	36
HD	49	9	10	4	4	27
NHL	50	21	21	29	32	103
LS	27	4	8	12	10	34
RCS	13	3	7	7	12	29
FL	10	10	3	1	2	16
OL	0	1	0	5	4	10
Probable	0	3	3	4	4	14
M	17	7	7	9	9	32

[a] NHL=non-Hodgkin's lymphoma.

Data collection is not yet complete, and data analysis is necessarily at a preliminary stage. The total numbers of new cases located thus far are shown in table 1. At the same time, investigators performing preliminary studies are preparing for the proposed expansion as detailed below, chiefly in the area of cell studies.

From 1976 to 1980, expansion is planned in several directions:

1) Establish a serum and tissue bank where sections and blood films are obtained on each case for use by a reference pathologist. Obtain serum from each patient and each household member or daily contact at the time of diagnosis and at 6-month intervals thereafter.

2) Characterize the cell type in all cases by means of in vitro procedures for several T- and B-cell markers when fresh specimens can be obtained or use sections stained either by periodic acid–Schiff (*23*) or immunoperoxidase (*7*) as a screening procedure.

3) Extend all clinical data, notably the first site in lymphomas and the date of appearance of the first symptom attributable to the disease in addition to the date of diagnosis.

4) Establish a control population (details are under discussion).

5) Develop further methods to detect space/time clustering of residence of cases during the changing residential pattern prior to diagnosis.

Some problems involved in this study are: The heterogeneity and scattered nature of the Tasmanian scene lead to difficulties in communication, and the close-knit social relationships make the study a delicate one. Desirable clinical and laboratory studies are difficult and often impossible in a widely scattered small population. Collection of personal data requires extensive resources, far more than are currently available to two small departments heavily committed to clinical responsibilities and undergraduate teaching. Nevertheless, the study appears to have significant potential.

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Cancer Registry in New Zealand [1]

Frank H. Foster [2]

ABSTRACT—Cancer registration, introduced in New Zealand in 1948, evolved from a clinically oriented to a population-based collection scheme. The registry, located within the National Health Statistics Centre, can draw on a wide range of other health data reported to that office. New Zealand has a population of 3 million, 8% of whom are Maoris. Findings indicated that cancer is the second leading cause of death and that Maori women have a much higher overall cancer death toll than other New Zealand women. Significantly higher incidence rates for cancers of the stomach, pancreas, lung, thyroid gland, and uterus and lower rates for cancer of the large bowel and melanoma of the skin were found in Maoris.—Natl Cancer Inst Monogr 47: 41–44, 1977.

The 3 million inhabitants of New Zealand are largely of British stock; less than half of the 8% classified as Maori are full Maori. Of the population, 48% live in cities of 100,000 or more.

Cancer is the second leading cause of death in New Zealand, next to heart disease and ahead of cerebrovascular disease. Among the Maoris, the cancer death rates at ages 35 years and over are significantly higher than in non-Maoris, due largely to a combination of delay in seeking treatment and a higher true incidence of cancer in certain sites. Table 1 lists site-specific incidence of cancer among the Maori and the non-Maori populations in 1972. A comparison of non-Maori and Maori cancer death rates in the period 1967–71 is also given (table 2). Of particular interest is the much higher overall cancer death toll in the Maori female.

Because the New Zealand public hospital system is funded by general taxation, patients pay no fees. A private hospital system, which provides 20% of New Zealand's available general beds, treats less than 5% of the people registered each year at the National Cancer Registry.

The Registry is located in the National Health Statistics Centre in Wellington. The Centre, part of the Department of Health, is responsible for a wide range of health statistics. It receives all death certificates, copies of all autopsy reports, and an individual abstract for each patient discharged from or dying in a public or private hospital throughout the country.

Cancer registration was established in New Zealand by the Department of Health in 1948 at the request of the British Empire Cancer Campaign Society (now the Cancer Society of New Zealand). Its first orientation was clinical, with registration limited to people under treatment for cancer in public hospitals or attending cancer consultation clinics. Death certificates were not used for registration unless the certificate stated that the deceased person had previously been treated for cancer in a public hospital; in these cases, the registry wrote to the hospital for staging, treatment, and histologic data. Death certificates for unregistered people were used to estimate total incidence. Cancers of all sites, including skin, were originally registered; in 1958 because of financial constraints, registration of skin cancers, other than malignant melanomas, was discontinued.

In 1965, an attempt was made to extend registration to patients treated in private hospitals by seeking the voluntary cooperation of clinicians and pathologists, but the response was sketchy and incomplete. However, by 1972, a national morbidity collection scheme was introduced to the entire private hospital system. Full coverage of private hospital cases was achieved by the end of 1973. Registration from all death certificates and from autopsy reports began in 1972, but registration derived from incidental findings at autopsy has been identifiable only since 1973.

From the beginning of 1974, the scope of Registry functions has broadened (i.e., has become population based), and all cancers (except basal and squamous cell skin cancers) treated in public and private hospitals, reported on death certificates, or reported as incidental autopsy findings are recorded. Objectives of the Registry are publication of data concerning: 1) the incidence of cancer in the New Zealand population by site, age, sex, ethnic group, and area of residence; 2) delay in seeking medical advice and beginning treatment; 3) extent of the disease when first treated; 4) methods used in the primary treatment; and 5) the overall survival rate in terms of site, age, and treatment. In addition, an objective

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

[2] National Health Statistics Centre, Department of Health, P.O. Box 6314, Wellington, New Zealand.

TABLE 1.—*Site-specific incidence of cancer among Maori and non-Maori populations, 1972* [a]

ICD[b]	Site	Rates/100,000 population[c] Maori[d]	Non-Maori
140	Lip	—	0.7
141	Tongue	X	1.3
142	Salivary gland	—	0.6
143	Gum	—	0.1
144	Floor of mouth	—	0.7
145	Other and unspecified parts of mouth	—	0.5
146	Oropharynx	—	0.4
147	Nasopharynx	—	0.2
148	Hypopharynx	—	0.3
149	Pharynx, unspecified	—	0.1
150	Esophagus	—	3.7
151	Stomach	30.1	11.0
152	Small intestine, including duodenum	X	0.9
153	Large intestine, except rectum	16.0	24.4
154	Rectum and rectosigmoid junction	4.6	12.8
155	Liver and intrahepatic bile ducts, specified as primary	5.7	1.1
156	Gallbladder and bile ducts	X	2.1
157	Pancreas	14.4	6.2
158	Peritoneum and retroperitoneal tissue	—	0.2
159	Unspecified digestive organs	—	0.1
160	Nose, nasal cavities, middle ear and accessory sinuses	—	0.4
161	Larynx	X	1.9
162	Trachea, bronchus, and lung	93.1	27.1
163	Other and unspecified respiratory organs	—	0.3
170	Bone	X	1.1
171	Connective and other soft tissue	X	2.0
172	Melanoma of skin	X	12.3
174	Breast	23.3	29.1
180	Cervix uteri	22.1	5.0
182	Uterus, other	7.6	6.6
183	Ovary, fallopian tube, and broad ligament	7.7	5.5
184	Other and unspecified female genital organs	X	1.0
185	Prostate	13.1	10.9
186	Testis	3.2	2.3
187	Other and unspecified male genital organs	X	0.4
188	Bladder	X	6.2
189	Other and unspecified urinary organs	8.8	4.3
190	Eye	X	1.4
191	Brain	4.4	5.1
192	Other parts of nervous system	X	0.5
193	Thyroid gland	7.4	1.9
194	Other endocrine glands	X	0.4
195	Ill-defined sites	—	0.4
196	Secondary and unspecified lymph nodes	X	0.9
197	Secondary malignant neoplasm of respiratory and digestive systems	X	1.4
198	Other secondary	5.6	0.6
199	Without specification of site	7.2	1.8
200	Lymphosarcoma and reticulum-cell sarcoma	3.2	3.2
201	Hodgkin's disease	X	2.7
202	Other neoplasms of lymphoid tissue	X	2.0
203	Multiple myeloma	4.5	2.6
204	Lymphatic leukemia	5.7	3.2
205	Myeloid leukemia	3.4	3.5
206	Monocytic leukemia	X	0.2
207	Other and unspecified leukemia	—	0.5
140–207	Total, all sites[e]	324.6	216.0

[a] Data were compiled for a report published by the National Health Statistics Centre.
[b] ICD=International Classification of Diseases (*1*).
[c] Rates have been standardized on the world population (*2*).
[d] —=no cases reported; X=less than 5 cases reported.
[e] Rates were not calculated for sites for which less than five registrations were reported.

TABLE 2.—*Comparison of non-Maori and Maori cancer death rates*[a]

Age, yr	Males Non-Maori	Males Maori	Females Non-Maori	Females Maori	Total Non-Maori	Total Maori
Under 5	11	13	9	12	20	25
5–14	8	9	5	6	13	15
15–24	10	16	6	12	16	28
25–34	20	26	17	31	37	57
35–44	51	70	65	112	116	182
45–54	158	197	182	316	340	513
55–64	457	714	333	618	790	1,332
65–74	1,010	1,150	571	907	1,581	2,057
75 and over	1,963	2,035	1,078	1,659	3,041	3,694
Sum of age-specific rates 0–74	1,725	2,195	1,188	2,014	2,913	4,209
Ratio of Maori to non-Maori	1.3:1		1.7:1		1.4:1	

[a] Values represent average annual rates/100,000 in age groups, 1967–71. Data were compiled for a report published by the National Health Statistics Centre.

of the Registry is to assist scientists by making registration data available for research purposes.

Data are reported to the Registry on cards designed for site-specific information. All cards require general data: demographic information, including occupation and ethnic group; hospital where initial diagnosis was made; hospital or clinic where patient is receiving treatment; date of first treatment; date of first symptoms; cause and date of death, including intercurrent deaths, i.e., cause of death was not attributed to the cancer for which the patient was registered; report of autopsy held; years of survival from date of first treatment; pathologic nature of growth; state of disease; treatment of primary malignant condition; and principal reason for no treatment. The basis of diagnosis is reported for cancers of the esophagus, stomach, trachea, bronchus, lung, mediastinum, breast, kidney, ureter, and bladder. For cancers of the cervix and uterus, smears are reported.

The New Zealand Cancer Registry system is a network of registers, maintained at 18 regional hospitals and usually operated by personnel in the medical records departments in consultation with medical staffs. For their work with cancer registration, the Cancer Society of New Zealand pays an annual supplement to registrars of the large hospitals who undergo a three-stage training program, with cancer registration discussed at the advanced level. Resident training courses also are held for medical records personnel, with one session on cancer registration and the application of such information as reported to the Registry. By supplementing the education of these hospital staff members in this way, the Society has helped to improve the timeliness of returns and standards of reporting.

The National Cancer Registry matches all death certificates against its register to effect entry of previously unregistered cases, to update the live register (comprised of those recorded cases who are still alive at the time of the update), and to establish whether those deceased registrants died of cancer or of an intercurrent disease (i.e., a condition other than the one entered in the records). National lists of cancer and intercurrent deaths are compiled by the registry each quarter and are distributed to each of the regional cancer registries, so that the names of those registrants with whom contact has been lost can be removed from the live registers.

Hospital abstracts are matched with Cancer Registry data to verify that all cancer inpatients have been properly registered. Autopsy reports are used to register cancers reported as incidental findings and to verify accuracy of data reported for previously registered cases. The International Classification of Diseases (*1*) is used to categorize diagnostic data in all collection procedures.

Current studies are:

1) The relationship between cancer incidence and organochloride insecticide residues. The study was prompted by John Copplestone, Vector and Biological Control, World Health Organization. The suggestion has been made that DDT, far from being a carcinogen, may in fact protect against carcinoma through its action as an inducer of hydroxylating enzymes. Copplestone was associated with a study that measured the levels of organochloride insecticide in adult New Zealanders during 1965–69. Two communities, one with a high and the other with a low level of residue, were identified, and the incidence of cancer found in each is now being studied.

2) A study of large bowel cancer was completed for the years 1964–68. A second 5-year study is now being done for 1969–73 that will provide data on occupation and geographic distribution of new registrations.

3) Incidence of cancer of the colon and rectum in North Canterbury residents is being reviewed in the Community Health Department at the Christchurch Clinical School. The Registry's role thus far has been primarily confined to casefinding.

4) The Geographical Departments of Auckland and Otago Universities are undertaking studies of the distribution of cancer in the New Zealand population from data supplied by the Registry. We are asking the Departments to examine ways of linking registration data to physical characteristics of regions, such as soil type and climate.

The National Cancer Registry issues an annual report, "Cancer Data," which is available on request. A 1-year delay between mortality and registration data has occurred because of the need to verify completeness of registration by linking notification with routine reports received from general hospitals. Linkage occurs some time after the hospital reports are received in the National Health Statistics Centre. In the past, we experienced lags because some hospitals delayed sending reports to the Centre. Since linkage cannot be completed until the last reports are received, it was expedient to publish registration data for the year preceding that for mortality data. The 1975 edition follows this pattern, i.e., data for 1972 mortality and 1971 notifications, but the 1976 edition will be oriented more toward registrations

and will contain 1972 and 1973 data. This improvement in timeliness results from giving public hospitals an incentive to send in reports more expeditiously.

The introduction to the 1974 report contains a commentary on the main features of the subsequent tables and also reviews of registrations of large bowel cancer during 1964–68 and those of malignant melanoma of the skin during 1949–68. The most interesting feature of the melanoma review was the substantial increases that occurred in age-specific rates throughout the 20-year period. For males and females, registration rates showed twofold or threefold increases for nearly all age groups. A similar pattern, though less marked in magnitude, also occurred in age-specific rates for deaths attributed to malignant melanoma.

The report includes three main sections. Data are shown for the total population and, in some tables, for the Maori population. In addition to current year data, some time series tables are shown.

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Cancer Epidemiology in the Philippines[1]

Generoso F. Basa, *M.D.*, Takeshi Hirayama, *M.D.*, *and* Antonia G. Cruz-Basa, *M.D.*[2]

ABSTRACT—Based on 16,492 cancer cases recorded at the Central Tumor Registry of the Philippines from July 1968 to June 1973, an epidemiologic analysis was conducted. Age-adjusted incidence rates for cancer of all sites in the Philippines, the United States, and Japan were similar. Cancers of the lung and breast were the leading sites in males and females, respectively. Age-specific incidence rates by each site were compared for the Philippines, the United States, and Japan. Cancers of the oral cavity, nasopharynx, liver, lung, breast, cervix, ovary, and thyroid and malignant lymphoma occurred with higher frequency in the Philippines. The more education people had, the more likely they were to develop cancers of the lung, pancreas, bladder, prostate, breast, and ovary, whereas cancers of the stomach, skin, esophagus, oropharynx, tongue, and mouth were more common in individuals who had not completed high school. Among smokers, neoplasms of the lung, larynx, tongue, mouth, liver, esophagus, and oropharynx occurred with significantly higher frequency. Epidemiologic implications and significance of these results for cancer control were discussed.—Natl Cancer Inst Monogr 47: 45–56, 1977.

Since we are an Asian people, the solutions to our indigenous health problems must be feasible. To assess realistically the cancer control program, one must first accept the current status of economic development and available resources in research and disease control in Asian countries. Secondly, one must consider Asian traditions and aspirations when mapping a strategy of human resources to meet this development. I believe the very essence of our convocation is to discuss problems inherent to the people in the Far East. Certain basic facts hold true for people everywhere. The history of a region not only sets the constraints of a milieu, but also highlights the assumption that human and economic resources in a region are the objects of, and the instruments for, change.

SITUATION IN ASIA

The current situation in most Asian countries can be summarized:

1) Some countries are becoming younger, so to speak, as indicated by the data on the age distribution of their population. Not only is the population increasing because of a decrease in communicable and infectious diseases and infant mortality, but longevity also is increasing.

2) Most of these countries are straining their resources to meet the health needs of this growing population. These demands include the pressure of existing communicable and infectious diseases and growing threats of chronic degenerative and neoplastic diseases.

3) Asian countries, by and large, are painfully aware of the need for medical facilities, training personnel, continuing medical education, and concerted efforts to check the migration of professionals that depletes the scientific capability of the country.

4) Economic underdevelopment in most countries apparently precludes the improvement of health services and disease control programs, particularly cancer control and research investigations.

The proportion of these factors will be accentuated by growing needs in the future. Some time ago, Western nations started an effective disease control program; now Asia must cope with its own problems including cancer control and research.

More than 7,000 islands comprise the Philippines, stretching about 1,100 miles northward from Borneo toward Taiwan. Scattered in the archipelago are 66 provinces, 59 cities, 1,369 municipalities, and 29,948 barangays (barrios). This 300,000-km^2 (117,180 square miles) region occupies 1.1% of the land area of Asia and accounts for 0.2% of the world's total land area. Although the Philippines is the 13th largest country in Asia, it ranks 6th in population and population density, following Taiwan, Korea, Japan, Sri Lanka, and India. The climate is tropical with four distinct seasons based on rainfall distribution. Like its neighbors Indonesia, Malaysia, and Polynesia, the Philippines can be characterized as a multilanguage nation. The country has 25 linguistic groups and 32 subgroups, making a total of 156 dialects.

Cities accommodate 15% of the population and comprise slightly more than 3.5% of the total land area. The other 85% of the people lives in

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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rural areas and depends on 1,500 government-supported rural health units, which serve 25,000 persons/unit. Approximately 440 units have no doctors, and only paramedical personnel staff the clinics. Government workers account for 24% of the total health personnel in the Philippines, and private physicians perform 65% of the outpatient hospital care.

POPULATION CHARACTERISTICS OF THE PHILIPPINES

The magnitude of the cancer problem in the Philippines is becoming apparent as communicable diseases are controlled more effectively. The increases in life expectancy and average age of the population and acceleration of industrialization and urbanization are closely related to the economic and social development of various parts of Asia.

The Philippines is a young country, with 47% of its people under 15 years of age and only 3% over 65. The population has increased from 10,445,300 in 1920 to 41,564,530 in 1974. With an annual birthrate of 3.01% in the years between 1970 and 1974, our population increase was more than 3 million (*1*). The extension of life-span is a great health accomplishment of the country. The average life expectancy at birth of every male and female has increased by 39.63 and 41.08 years, respectively; neonatal, infant, and maternal death rates have decreased by 28.8, 62.2, and 75.6%, respectively. If this trend continues and the population experiences prolonged exposure to new environmental hazards, we can expect a corresponding rise in chronic degenerative diseases and cancer.

CANCER CONTROL PROBLEMS

Cancer mortality has risen from the 10th cause of death in the Philippines in 1953 to the 7th in 1968 (*2*). Cancer mortality statistics reveal a 5-year average of 23.5/100,000 population, constituting 3.8% of all deaths. Although cancer is a reportable disease, deficiencies in registration occur because of geographic barriers of nonadjacent islands, linguistic diversities, difficulties in communication, deficiencies in medical manpower and hospital facilities, and a lack of pervasive public education. Underregistration of cancer cases is common in all regions.

To facilitate correction of these problems, geographic classification was introduced. The country has been divided into eight regions, which include 66 provinces and 59 cities (text-fig. 1). Most neoplastic diseases are registered efficiently in region III, where the Greater Metropolitan Manila provinces and cities are situated. The farther the region is located from this developed area, the less likely it is that cancer cases would be reported.

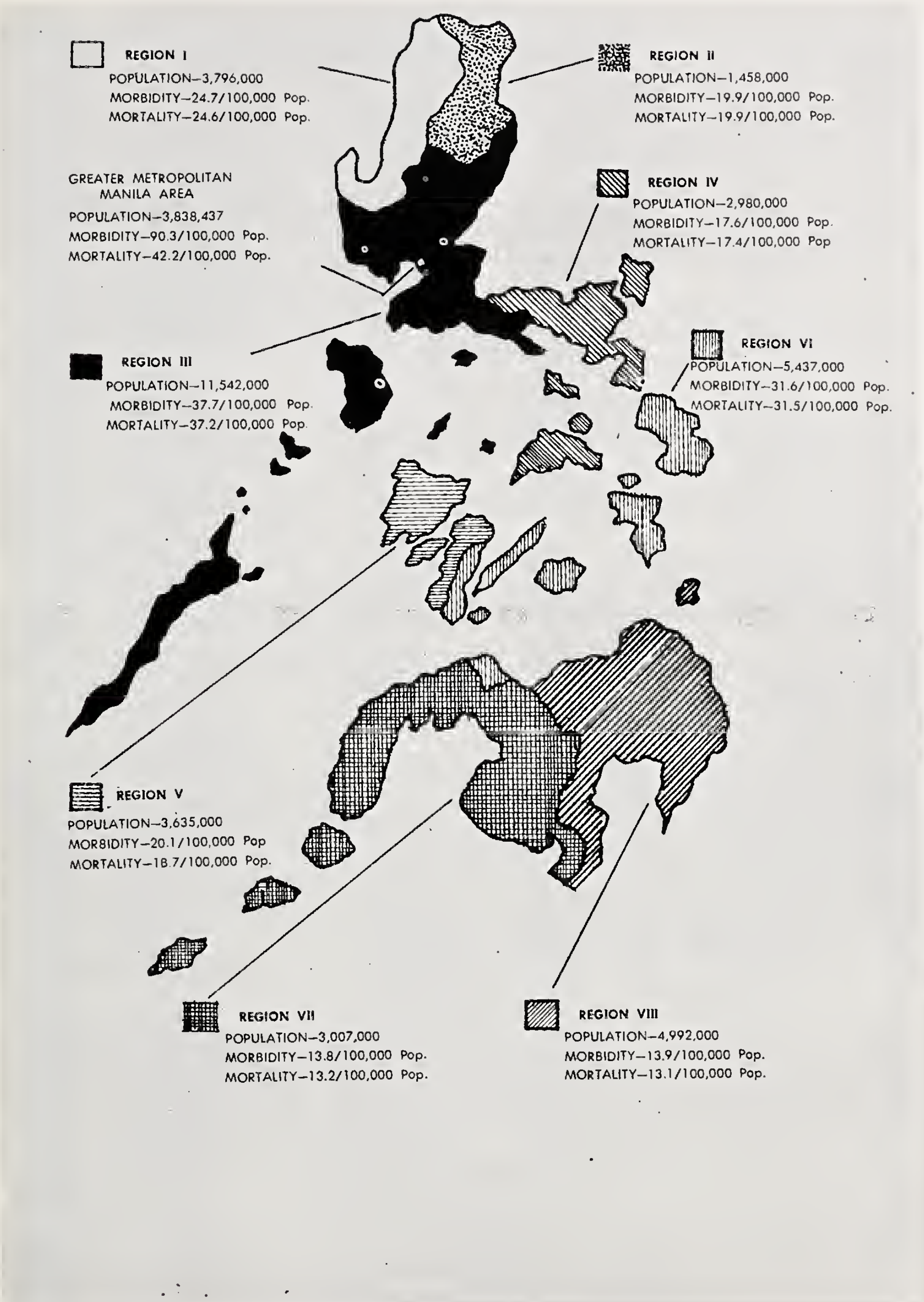
Only 57 private and 42 Government hospitals provide the 7,074 beds in the Greater Metropolitan Manila area. None of the 19 subspecialty hospitals is devoted to the care of patients with cancer. Private practitioners manage 29.2% of the cancer patients and medical centers provide care for 35.7%. In region III, private doctors treat 21.8% of the cancer patients and hospitals, 25.5%. Government health officers attend cancer patients in the most remote areas.

The number of patients in a defined population depends on the detection and diagnosis of cancer by medical doctors. Where medical resources and trained physicians are limited, as they are in the seven other regions, the magnitude of the problem is understated. Except for one in the Greater Metropolitan Manila area, no hospital registry system has been developed. In the rest of the country, we have no facilities for cancer detection and diagnostic procedures, except for isolated facilities in private and government hospitals in cities. This situation accounts for the shift of cancer patients from their communities to medical centers in the Metropolitan Manila area. In communities without these facilities, cancer may not be diagnosed until autopsy, or is missed. Cancer mortality rates for Greater Metropolitan Manila, region III, and the whole country vary from the cancer incidence rates recorded by the Central Tumor Registry of the Philippines. These incidence rates were obtained from 24 participating hospitals in Greater Metropolitan Manila from 1968 to 1972.

THE CENTRAL TUMOR REGISTRY OF THE PHILIPPINES

To study the size and nature of the cancer problem in the Philippines, the Philippine Cancer Society and the Department of Health of the Republic of the Philippines jointly established a Central Tumor Registry in 1968.

We conducted an epidemiologic study based on registry data obtained between July 1968 and June 1973. This report is preliminary. In late 1975, we began an analytical epidemiologic study of cancer, in which we focused our attention on neoplasms of the breast, cervix, and lung.



TEXT-FIGURE 1.—Cancer morbidity and mortality rate/100,000 population for eight health regions.

MATERIALS AND METHODS

Hospital cancer registries are usually located in the Medical Records Department of hospitals, with registry secretaries having access to all records of inpatients and outpatients. These secretaries are responsible for abstracting case histories and follow-up reports of patients. Abstracts, submitted every month, are reviewed by the staff of the Central Tumor Registry, and discernible problems are resolved before the abstracts are coded, indexed, cross-checked, and analyzed. Computerization of all records is now under negotiation.

Close liaison was promoted between hospital registrars and the Central Tumor Registry. Twenty-six leading hospitals in the Philippines participated in the registry; 24 of the hospital-based registries were located in the Greater Metropolitan Manila area.

Between July 1968 and June 1973, detailed analysis was obtained for the 16,492 cases of malignant neoplasms [International Classification

TABLE 1.—*Annual cancer incidence per 100,000 population by age, sex, and first 10 leading sites* [a]

Form of cancer	Sex [b]	Age group, yr															
		0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75+
Cancer of all sites	M	6.35	6.06	8.76	18.33	14.19	22.37	34.32	70.51	130.98	203.21	307.21	453.96	534.00	894.44	855.14	919.28
	F	10.43	3.75	9.22	14.88	15.57	35.99	72.10	163.82	262.90	369.34	525.09	508.84	579.33	628.89	846.22	591.37
Oral cavity	M	—	0.19	0.16	—	0.63	1.11	1.92	4.01	8.77	7.13	23.65	48.11	78.49	86.76	89.98	125.02
	F	0.09	—	0.11	0.72	0.42	1.33	0.79	2.94	7.62	7.55	35.18	32.56	58.51	59.11	156.55	88.70
Nasopharynx	M	—	—	0.77	1.04	1.78	1.90	2.84	9.65	14.14	24.04	27.64	35.40	27.23	33.09	8.55	35.85
	F	—	—	—	0.55	0.59	1.76	2.66	6.22	6.83	7.01	12.67	12.72	11.58	14.46	16.92	11.23
Stomach	M	0.5	0.06	0.08	0.12	0.15	0.55	1.13	4.23	7.46	9.98	24.88	31.77	44.85	63.50	83.80	84.59
	F	—	—	0.11	0.09	0.10	1.11	2.01	1.96	6.59	9.60	10.50	21.37	28.96	27.67	41.46	28.97
Colon and rectum	M	0.15	0.06	0.16	0.91	0.88	3.57	2.74	6.29	11.65	24.85	20.58	38.58	49.12	93.02	80.38	103.89
	F	—	—	0.11	0.26	0.84	0.64	1.29	4.58	4.99	10.71	15.75	16.79	23.17	20.12	44.84	23.65
Liver	M	0.10	—	0.08	0.38	0.39	2.46	3.77	8.24	16.37	23.02	27.03	45.58	36.84	70.66	22.23	41.36
	F	0.09	0.14	0.11	0.35	0.11	0.75	1.87	2.78	5.78	8.86	11.02	8.65	6.37	13.83	33.84	23.06
Lung	M	—	—	0.08	0.38	0.89	1.45	3.19	10.92	22.39	38.09	60.21	63.10	66.75	136.84	129.99	84.57
	F	—	—	—	—	0.17	0.64	1.29	4.58	4.99	10.71	15.75	16.79	23.17	20.12	44.87	23.65
Prostate	M	—	—	—	—	—	—	5.49	—	0.78	2.24	7.68	17.25	35.24	84.67	116.29	147.08
Thyroid	M	—	—	0.08	0.65	0.31	0.78	1.37	1.97	2.48	5.09	3.68	13.16	10.14	10.73	8.55	11.95
	F	—	—	0.55	1.56	2.22	5.36	6.34	10.48	11.56	16.98	18.90	24.93	17.95	50.30	16.92	7.09
Malignant lymphoma	M	0.30	0.86	1.36	2.78	2.44	2.57	3.89	5.00	7.98	11.40	18.12	25.87	32.59	32.19	33.35	23.90
	F	0.40	0.36	0.44	1.10	1.38	1.87	3.17	1.47	5.52	5.17	5.77	12.21	13.90	14.40	26.33	20.10
Leukemia	M	1.27	1.92	1.71	3.04	1.70	0.89	1.92	2.60	3.53	2.64	1.22	4.53	1.60	3.57	6.84	10.31
	F	2.25	1.08	2.66	1.65	1.07	1.76	1.00	0.16	1.05	3.32	1.57	1.08	1.73	1.25	1.69	10.05
Breast	F	—	—	0.22	0.63	1.32	7.34	24.00	60.77	95.69	141.45	176.95	153.66	145.99	148.41	150.62	94.61
Cervix	F	—	—	—	—	0.35	2.87	9.80	34.40	57.83	76.45	100.81	82.43	72.41	74.83	66.00	41.98
Ovary	F	0.29	—	0.55	1.84	1.93	2.87	3.46	7.86	11.56	21.05	26.77	18.31	26.06	23.89	26.23	5.32

[a] Data reproduced from (*3*) with the permission of the publisher.
[b] M=male; F=female.

TABLE 2.—*Relative frequency of cancer by sites and sex (1968–73), Greater Metropolitan Manila area*[a]

ICD No.	Site	Male		Female	
		Total No.	Percent	Total No.	Percent
140–208	All sites	6,771	100.00	9,721	100.00
140	Lip	43	0.64	28	0.29
141	Tongue	176	2.60	125	1.28
142	Salivary gland	70	1.03	76	0.78
143–145	Mouth	294	4.34	378	3.89
147	Nasopharynx	488	7.21	251	2.58
149	Other pharynx	16	0.24	6	0.06
150	Esophagus	110	1.63	85	0.87
151	Stomach	443	6.54	287	2.95
152	Small intestine	52	0.77	26	0.27
153	Colon	276	4.08	211	2.17
154	Rectum	288	4.25	192	1.98
155	Liver				
156	Gall bladder, etc.	541	7.99	213	2.19
	Liver, secondary				
157	Pancreas	120	1.77	70	0.72
160	Nose, sinuses, etc.	19	0.28	15	0.15
161	Larynx	151	2.23	39	0.40
162–163	Bronchus, trachea, lung	912	13.47	289	2.97
170	Bone	271	4.00	241	2.48
171	Connective tissue	114	1.68	95	0.98
171	Melanoma, skin	290	4.28	227	2.34
173	Other skin				
174	Breast	30	0.44	2,811	28.92
180	Cervix uteri	—	—	1,489	15.32
181	Other uterus	—	—	70	0.72
182	Corpus uteri	—	—	421	4.33
183	Ovary	—	—	478	4.92
184	Other female genital	—	—	75	0.77
185	Prostate	347	5.13	—	—
186	Testis	90	1.33	—	—
187	Other male genital				
188	Bladder	161	2.38	66	0.68
189	Kidney	131	1.94	100	1.03
190	Eyes	64	0.95	64	0.66
191–192	Brain, nervous system	109	1.61	66	0.68
193	Thyroid	134	1.98	519	5.34
194	Other endocrine	7	0.10	6	0.06
200–202	Lymphosarcoma and Hodgkin's	441	6.51	255	2.62
203	Multiple myeloma	28	0.41	21	0.22
204–207	Leukemia	208	3.07	167	1.72
	Others	347	5.13	259	2.66

[a] Data are reproduced from (*3*) with the permission of the publisher.

of Diseases (ICD) No. 140–204] registered (tables 1, 2). Of these, 75.8% were diagnosed by histopathology, and 24.2% were diagnosed clinically. Review of the records revealed that 55.5% were localized, 25% had regional involvement, and 18.1% included remote metastasis; the remainder were indeterminate.

RESULTS

Crude and Adjusted Age Incidence Rates

Total incidence of cancer is defined as all newly reported neoplasms among residents in Greater

TABLE 3.—*1970 Population of Greater Metropolitan Manila*[a,b]

Age group, yr	Both sexes	Male	Female
0–4	577,268	299,474	277,794
5–9	444,147	230,976	213,171
10–14	366,807	182,452	184,355
15–19	429,765	174,523	255,242
20–24	480,929	211,351	269,578
25–29	370,485	178,782	191,703
30–34	294,189	148,561	145,628
35–39	214,794	109,196	105,598
40–44	158,511	78,633	79,878
45–49	127,266	62,827	64,439
50–54	101,283	47,198	54,085
55–59	82,154	38,329	43,825
60–64	61,694	29,588	32,106
65–69	39,626	18,000	21,626
70–74	23,159	11,460	11,699
75–Up	24,913	10,878	14,035
Not stated	1,286	495	791
Total	3,798,276	1,832,723	1,965,553

[a] Composition of Greater Metropolitan Manila: 1) Manila, 2) Caloocan City, 3) Pasay City, 4) Quezon City, 5) Las Piñas, 6) Makati, 7) Malabon, 8) Mandaluyong, 9) Marikina, 10) Navotas, 11) Parañaque, 12) San Juan, and 13) Valenzuela.
[b] Data were taken from (*4*).

Metropolitan Manila. Diagnosis was obtained through review of hospital records, autopsy, histopathology, radiology, and other clinical means. Diagnoses based on death certificates comprised only 9.2% of total cancers reported. The first 10 leading sites of cancer registered in the Central Tumor Registry of the Philippines are listed in table 1. Cancer incidence among females was generally much lower than those in males, except in the age group between 28 and 62 years.

Population data for 1970 were obtained from the Advanced Report on Population and Housing (table 3) (*4*).

In 1970, 3,343 cases were on record in a population of 3,798,276, yielding an incidence rate of 88.01/100,000 population. In males, the figure was 75.02 (1,375 cases from 1,832,723) and in females, it was 100.12 (1,968 cases from 1,965,553).

To compare incidence rates on population-based registries, we used the Connecticut incidence rates for 1963 to 1965 as reported by the Connecticut Tumor Registry (*5*) and incidence rates for 1966 as reported by the Okayama Prefectural Cancer Registry in Japan (*6*). As does any population-based registry, we collected main cancer incidence data from hospital reports verified either by histopathology, radiologic or clinical facilities, autopsies, and death certificates. One reason for undertaking this comparative study was to determine the effects on cancer incidence of "Westernization" of life-style and cultural exposure on one hand, and the influence of the

TABLE 4.—*Cancer incidence rate/100,000 population by site and geographic area*

Site	Sex	Philippines (Greater Manila, 1970)	United States (Connecticut, 1963–65)	Japan (Okayama, 1966)
Cancer of all sites				
Crude incidence rate	M	75.02	300.1	213.7
	F	100.12	281.7	170.3
Adjusted incidence rate[a]	M	75.02	111.7	87.0
	F	100.12	113.7	75.1
Mouth	M	14.6[b]	4.0[b]	0.7[b]
	F	13.4	1.4	0.3
Nasopharynx	M	9.3	0.5	0.4
	F	4.2	0.1	0.0
Stomach	M	11.1	14.7	93.9
	F	6.1	6.8	45.7
Colon and rectum	M	14.2	43.0	11.3
	F	5.8	37.4	9.1
Liver	M	11.4	4.2	0.3
	F	4.0	3.6	0.4
Lung	M	21.3	44.0	15.3
	F	5.7	7.8	5.2
Prostate	M	10.8	33.0	4.3
Breast	F	50.3	62.3	12.4
	M		0.5	0.7
Cervix	F	26.6	10.3	22.4[c]
Ovary	F	7.7	11.3	2.8
Thyroid	M	2.7	0.8	1.1
	F	8.2	3.0	3.3
Malignant lymphoma	M	7.9	8.8	2.7
	F	4.1	5.8	1.2
All sites	M	150.3[a]	257.8	189.3
	F	177.4[a]	220.0	145.4

[a] Data are adjusted to greater Manila rates for 1970.
[b] Data are adjusted to world population.
[c] *Value* includes in situ cancer.

Philippines' Asian neighbors on the other. The heterogeneous population-at-risk in the Greater Metropolitan Manila area had the greatest exposure to these factors.

As shown in table 4, crude incidence rates for cancer in Greater Metropolitan Manila were far lower than in Connecticut and Okayama. However, the age-adjusted incidence rate (adjusted to the age composition of the Greater Metropolitan Manila population) was similar to the rate in Connecticut and Okayama. For females, the rate in Greater Metropolitan Manila was even higher than that in the Okayama Prefecture.

These statistics clearly indicated that the cancer problem in the Philippines is just as serious as in other developed countries and that our apparently lower incidence is but a reflection of the younger age of the population. Probably, as the age of the population increases in the future (as a result of reduced mortality from communicable diseases), cancer incidence rates will approach or surpass those of Japan or the United States.

Cancer Pattern in the Philippines

From 1968 to 1973, 16,492 cases of cancer were documented from information collected from 24 participating hospitals in the Greater Metropolitan Manila area (table 2). These cases were classified according to site. The most common site in males was in the lung (13.5%), followed by liver (8.0%), nasopharynx (7.2%), and stomach (6.5%). In females, the leading site was in the breast (28.9%), followed by cervix uteri (15.3%), thyroid (5.3%), ovary (4.9%), and corpus uteri (4.3%).

Age-specific Incidence Rate

Age-specific incidence rates for cancer of all sites were calculated for Greater Metropolitan Manila and, when compared with those for Connecticut and Okayama, revealed the following:

1) All sites
   - Male: No significant difference was noted in patients aged 30 to 55. Rates in the Philippines were lower in persons over 55 and under 15.
   - Female: No difference was observed between the Philippines and the United States, but rates were higher in the Philippines than in Japan for ages 25–55. Rates for age 56 and above and age 15 and below in the Philippines were similar to those of Japan.
2) Oral cavity
   - Male: Incidence was higher in the Philippines than in the United States and much higher than in Japan.
   - Female: Many more cases were seen in the Philippines than in the United States or Japan.
3) Nasopharynx
   - Male: Rates were much higher in the Philippines than in the United States or Japan.
   - Female: Many more women were affected in the Philippines than in the United States or Japan.
4) Stomach
   - Male: Rates were much higher in Japan, but those in the Philippines resemble those of the United States, with a slight increase in the 20- to 40-year bracket.
   - Female: Though incidence was much higher in Japan than in the Philippines, ours was higher than in the United States.

5) Colon and rectum
 Male: Again, much higher in the United States for age 30 and above, but rates in the Philippines were slightly higher than in Japan for age 30 and above; they were lower below the age of 30.
 Female: Rates were much higher in the United States for women age 40 and above; however, those in the Philippines were similar to those in Japan.

6) Liver
 Male: Rates in the Philippines were similar to those in Japan and higher than those in the United States.
 Female: Though rates were higher in the Philippines for women under 50; after 55, they were higher in Japan.

7) Lung
 Male: Rates in the Philippines resemble those in the United States and are much higher than in Japan, except for age 60 and above.
 Female: Incidence was higher in the United States for ages 40–60, otherwise little difference was recorded among the three countries.

8) Breast
 Female: Rates in the Philippines were similar to those in the United States, and much higher than in Japan.

9) Ovary
 Rates in the Philippines resembled those in the United States, but were much higher than in Japan.

10) Cervix uteri
 Rates in the Philippines were higher than in Japan and far higher than in the United States.

11) Prostate
 Rates in the Philippines were between those in the United States and Japan.

12) Thyroid
 Male: Rates in the Philippines were higher than those in Japan and much higher than in the United States.
 Female: Rates in the Philippines were much higher than those in Japan or the United States.

13) Malignant lymphoma
 Male: Rates in the Philippines were similar to or higher than those in the United States for ages 40 and above, and much higher than Japan in all age groups.
 Female: Rates in the Philippines were similar to the United States but lower in the younger age groups. Rates in Japan were low.

According to the 1970 national census figures, 46,442 Chinese (54.3% of the total alien population in the Philippines) were living in the Greater Metropolitan Manila area. The Chinese community constituted 15.7% of the total Greater Metropolitan population-at-risk of 3,798,276. This was a 50% drop from the 1960 population. Naturalization of adults and their families and an apparent lack of new migrants from China (most of the Chinese came from the province of Fookien) seemed to be the main factors in this decline. In addition, many aliens moved to Western countries. Other minority nationalities were usually transients and nonresidents. A comparative study of the 10 leading causes of deaths in Manila disclosed that 16.73% of the total deaths were among Chinese.

Mortality data of patients with nasopharyngeal and liver cancers were similar among Filipino and Chinese males, but much higher among Filipino females than their Chinese counterparts; breast and stomach cancers, however, appeared to be more common among Chinese women. Reports of death from cervical cancers were unreliable because physicians signing death certificates often include cervical with other uterine cancers. Thus figures for unspecified uterine cancer are often higher than for cervical cancer.

Sociologic Factors

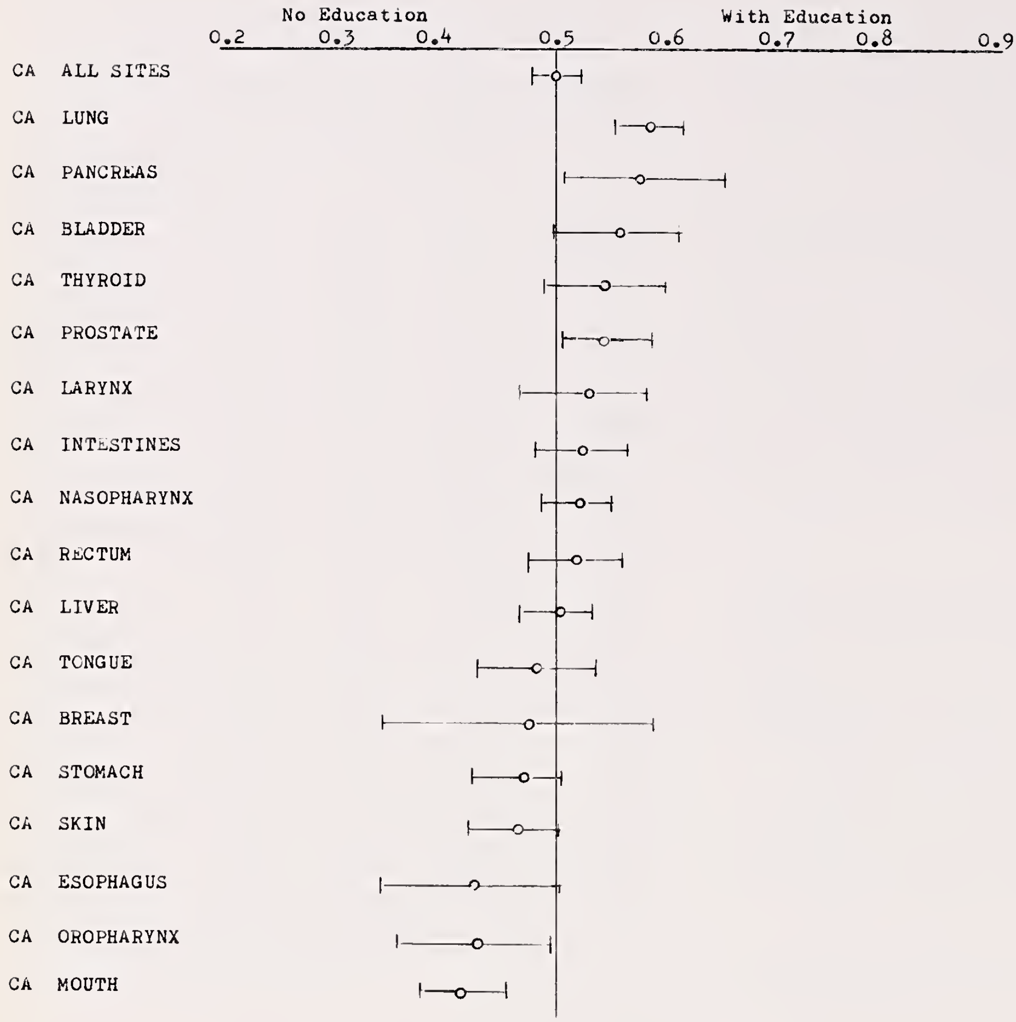
Education

Variations in frequency among different sites according to the patient's educational background were significant (text-figs. 2, 3). Ridit analysis demonstrated the following findings:

 Male: Cancers of the lung, pancreas, urinary bladder, and prostate were significantly more common in men who completed high school and college; cancers of the stomach, skin, esophagus, oropharynx, and mouth were significantly more frequent in less educated men.
 Female: Cancers of the lung, ovary, and breast were found in significantly higher frequency in more highly educated women; cancers of the oropharynx, tongue, and mouth were significantly more common in women who had not completed high school.

Occupation

Frequency of cancers among patients with outdoor and indoor occupations was compared for



TEXT-FIGURE 2.—Cancer and different educational levels of men. Data from Central Tumor Registry of the Philippines, Philippine Cancer Society.

different sites; relative risk was also calculated (table 5).

Male: Outdoor workers had significantly higher relative risk for cancers of the oropharynx and mouth.

Female: Outdoor workers had significantly higher relative risk for cancers of the oropharynx, mouth, tongue, and liver.

Smoking

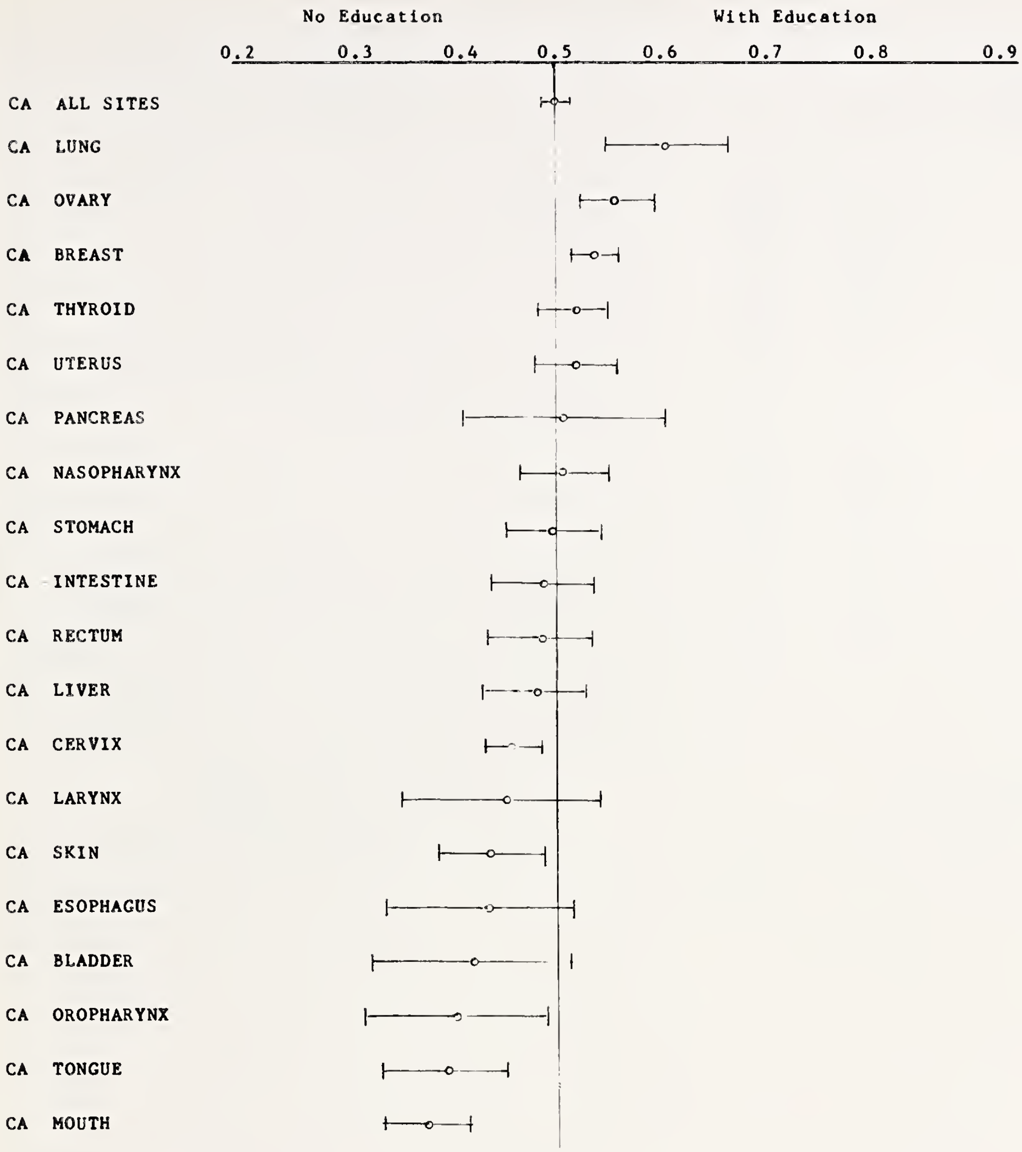
History of smoking accounted for significant variation in frequency among different cancer sites (text-figs. 4, 5). Chi-square test and relative risk calculations revealed the following results:

Male: Significantly higher relative risk for cancers of the lung, larynx, tongue, and skin was observed in current smokers. When data of ex-smokers were added to those of current smokers, cancers of the lung, larynx, tongue, and liver showed significantly higher relative risk.

Female: Significantly higher relative risk was observed in current smokers for cancers of the mouth, tongue, esophagus, lung, liver, and rectum. When data of ex-smokers were added to those of current smokers, cancers of the mouth, tongue, esophagus, liver, larynx, rectum, intestine, oropharynx, and lung showed significantly higher relative risk.

DISCUSSION

The characteristic pattern of cancer revealed by this study is significant from the aspects of epidemiologic research and control strategy programming. Cancer control activities should be emphasized for those sites showing significantly higher frequency in the Philippines than other countries. These include cancers of the oral cavity,



TEXT-FIGURE 3.—Cancer and different educational levels of women. Data from Central Tumor Registry of the Philippines, Philippine Cancer Society.

nasopharynx, liver, and lung and malignant lymphoma in males and cancers of the oral cavity, nasopharynx, liver, breast, cervix, ovary, and thyroid in females. The higher frequency of oral cancer, especially in the lower socioeconomic strata, must be due to the chewing of buyo betel nut (areca leaves with lime) alone or in combination with smoking.

Cancer of the nasopharynx, which is common in Chinese, also occurs frequently in Filipinos. The possible role of herpes type virus (Epstein-Barr virus) as studied in Taiwan, Japan, Hong Kong, Singapore, and East Africa, should be explored. Immunogenetic markers such as human leukocyte antigen and the immunovirologic effects of Epstein-Barr virus are relevant to nasopharyngeal tumors, especially when one considers the direct contact of Chinese migrants in the Philippines for centuries.

Cancer of the liver is now considered closely associated with the hepatitis B (HB) antigen (Australia antigen). The relationship between HB virus and hepatocellular carcinoma is supported by consonance between ethnic variation of hepatoma incidence and the prevalence of HB virus carriers in some ethnic groups. Studies conducted in the Philippines have already revealed a close association between the HB antigen-positive rate and primary hepatoma. In the Philippines, the HB antigen-positive rate is 16.1% when the immunoadherence method with standardized reagent is used, compared with the rate of 18.0% in Papua New Guinea, which is the highest, and 0.5% in Australia, which is the lowest in the Western

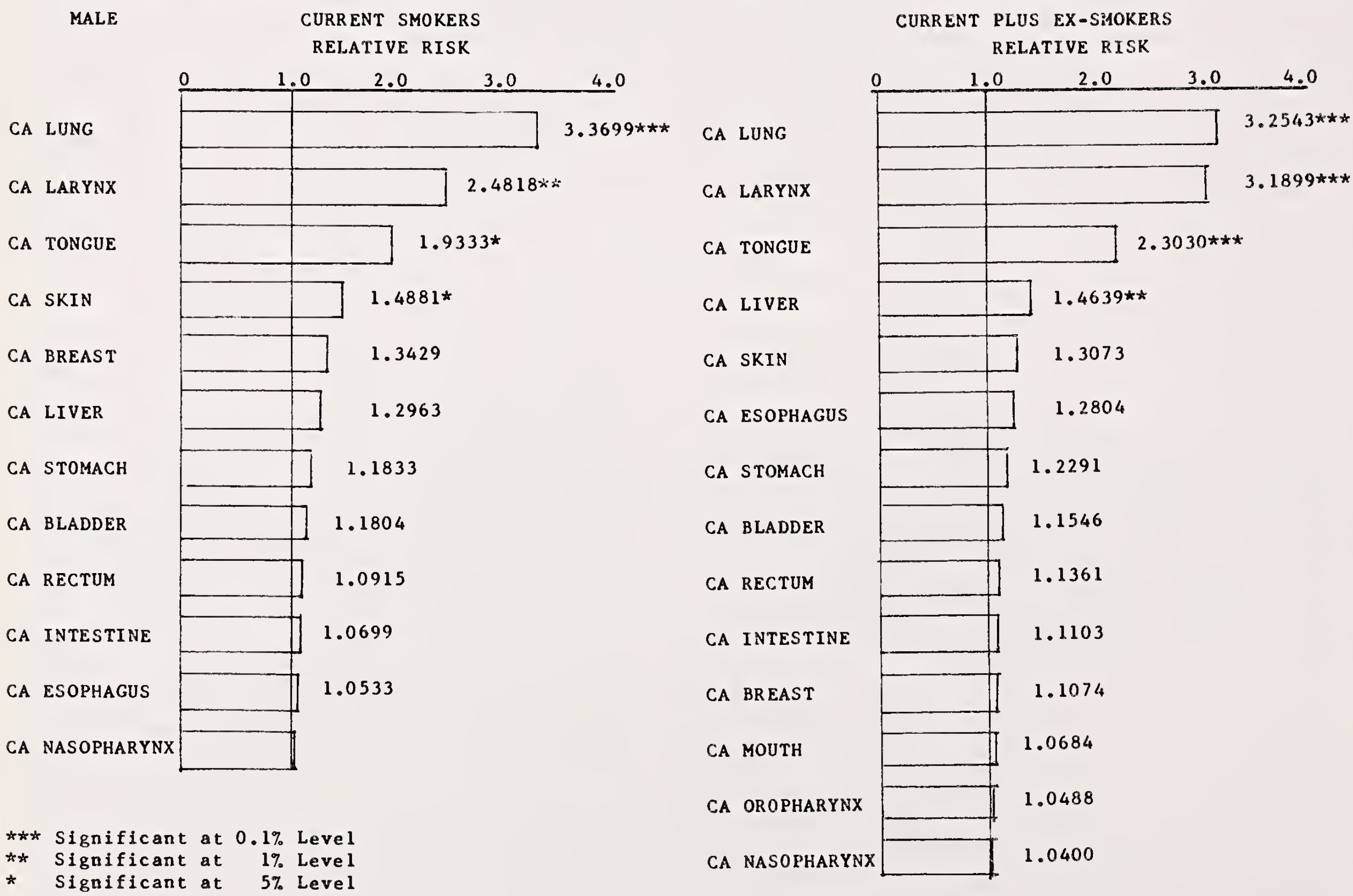
TABLE 5.—*Cancers showing higher relative risk among outdoor workers*

Cancer sites	No. of outdoor workers	No. of indoor workers	Relative risk	χ^2
Males				
Oropharynx	42	2	8.9423	12.1839 [a]
Mouth	119	25	2.0484	10.1072 [b]
Tongue	79	21	1.5963	3.1807
Breast	11	3	1.5384	0.1381
Skin	98	29	1.4341	2.5156
Nasopharynx	213	69	1.3231	3.5294
Liver	172	69	1.0477	0.0583
Prostate	97	39	1.0436	0.0155
Cancer all sites	2,280	055		
Females				
Oropharynx	6	1	7.9898	3.6160
Mouth	30	7	5.8528	20.7191 [a]
Tongue	14	4	4.6951	7.5680 [b]
Esophagus	8	3	3.5532	2.8506
Bladder	4	2	2.6539	0.5734
Liver	21	12	2.3507	4.9843 [b]
Rectum	18	14	1.7107	1.7985
Cervix	115	127	1.2313	2.0651
Thyroid	41	51	1.0669	0.0372
Stomach	22	29	1.0036	0.0171
Cancer all sites	793	1,049		

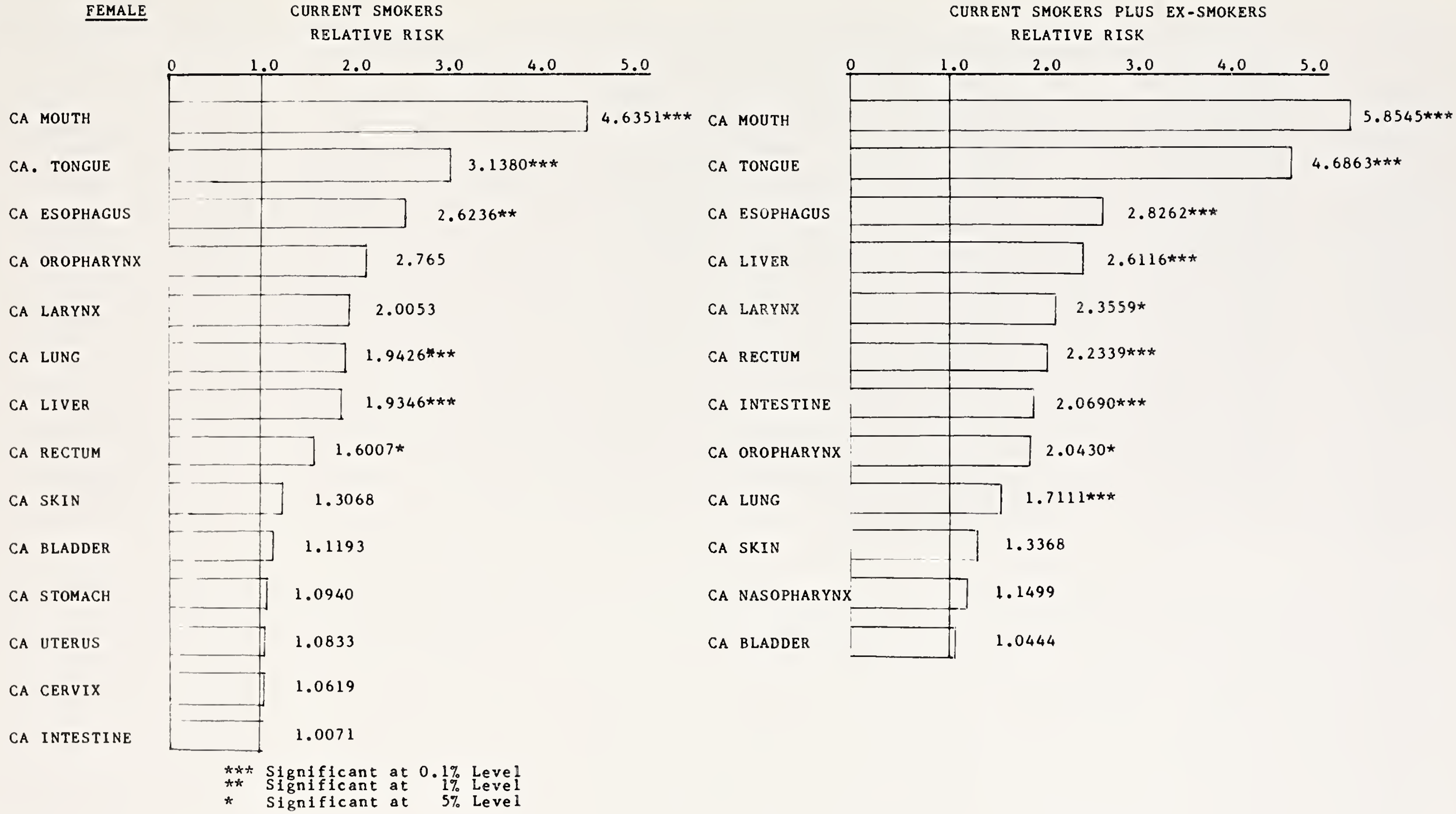
[a] Value is significant at 0.1% level.
[b] Value is significant at 1% level.

Pacific area. The prevalence of HB virus is higher in Asia than in the normal population. Subtype ADW by passive hemagglutination inhibition test is present in the Philippines, Kenya, East African countries, and Indonesia (*7*). Influence of food contamination by microtoxin (especially aflatoxin) is also implicated in liver cancer. The close relationship of aflatoxicosis with liver carcinoma and the report of a high frequency of liver cancer in certain parts of the country, notably in the Visayas and some parts of northern Luzon, require further epidemiologic studies. Reports reveal a high contamination with aflatoxin in cereals and major food items in these regions.

Cigarette smoking is a well-known risk factor for cancer of the lung. A recent study on the effects of a cigarette shortage in Japan during and after World War II, a period of 10 years or more, disclosed a downward trend in the mortality rate compared with that in the United States during the same period. An antismoking campaign similar to this social experiment was described (*8*) as the best operational strategy for



TEXT-FIGURE 4.—Cancer showing higher relative risk among smokers (risk in nonsmokers = 1.0). Taken from Central Tumor Registry of the Philippines (1968–73), Philippine Cancer Society.



TEXT-FIGURE 5.—Cancer showing higher relative risk among smokers (risk in nonsmokers = 1.0). Taken from Central Tumor Registry of the Philippines (1968–73), Philippine Cancer Society.

coping with the problem. The increased frequency of lung cancer that occurs in persons belonging to the upper socioeconomic strata probably reflects the high consumption of cigarettes, which are still expensive for people in the country. The Metropolitan Manila area probably has the most critical air pollution problem, but it is still within tolerable limits. Suspended particles exceeded 500 $\mu g/m^3$ of air, according to occasional monitoring. Sulfur dioxide concentration exceeded the limits established in the United States and Japan (*9*).

The reason for the higher frequency of malignant lymphoma in the Philippines is not known. Immediate studies are needed to determine virus involvement, especially the herpes type. Extensive programs for epidemiologic study are needed to explain the higher frequency of cancers of the breast and ovary in this country. These cancers occur more frequently in more highly educated women. In a later report, we will review associations with such factors as diet, menarche, age of first marriage, number of pregnancies, and length of breast feeding. The higher frequency of cervical cancer in the Philippines compared with other developed countries probably is influenced by sexual hygiene. The increased frequency of thyroid cancer also requires epidemiologic studies, especially to determine its relationship to metabolic thyroid disorders that are endemic in certain regions.

Organized epidemiologic research based on multiple disciplines is urgently needed at this time. This study clearly reveals the significance and importance of the Philippine Central Tumor Registry, which not only serves most of the leading hospitals in the country, but also centralizes valuable epidemiologic information.

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Current Status of the Cancer Registry and Population-Based Studies in Hong Kong[1]

J. H. C. Ho[2,3]

ABSTRACT—Despite the handicaps of shortage of staff, lack of a broad health insurance program, and the apathy of most of the medical profession, we managed to establish a Cancer Registry that is achieving near completeness in registration of cancers at certain sites. These cancers are among the most common types occurring in the population.—Natl Cancer Inst Monogr 47: 57–60, 1977.

ESTABLISHMENT OF A CANCER REGISTRY

Hong Kong has had one of the most, if not the most, rapid rates of population increase in the world, largely due to heavy immigration. At the end of World War II, the population was estimated at approximately 600,000. Now it is close to 4.5 million. Even before the war, during the decade 1921–31, the increase was 34%. Therefore, the Government had to deal with such urgent problems as housing, medical care, education, and employment; as a result, the operation of a cancer registry was given a low priority. In the control of diseases, emphasis is placed on those that are communicable.

A Cancer Registry formed within the Medical and Health Department Institute of Radiology and Oncology in 1963 became fully operative in 1965 when it produced its first annual report. A consultant in radiology and oncology, who has a personal interest in cancer epidemiology, has been in charge of the Institute. His staff consists of three clerks and a part-time statistician. Although the staff has not increased since the Institute was formed, one of the clerks was sent (with the financial help of the International Agency for Research on Cancer) for a short training period in cancer registry work at the National Cancer Center (Dr. T. Harayama's department) in Tokyo. Another clerk had some formal training in elementary medical statistics in Hong Kong. The work is made more difficult by the fact that cancer notification, unlike that for communicable diseases, is on a voluntary basis. Our Government is reluctant to increase the paperwork for our practicing physicians, who are overloaded with clinical commitments. Hong Kong has about one registered doctor for every 1,700 people. Voluntary notification is never satisfactory as most doctors loathe to fill out forms of any kind; their chief concern is the care of patients. In 1965, the person in charge had to make a special effort to collect data from doctors who would not normally notify the Registry of their cancer cases. During the following 3 years (1966–68), he could not continue the data collection because of pressure of other work. In 1969, a new approach was adopted. Instead of relying entirely on voluntary notification from attending physicians and surgeons, registry clerks were sent to collect data from hospital records of patients' admissions and discharges. In addition, they collected material from the registers of histopathologic examinations kept by the departments of pathology.

Objective of the Cancer Registry

With such a small, largely untrained staff, only modest objectives can be entertained. One of the main objectives is to achieve as high a rate of registration of new cases as possible to obtain detailed incidence rates of cancers according to their anatomical sites and cells of origin; another goal is to provide a basis for comparative geographic incidence and epidemiologic studies.

Logistics

The channels through which the necessary information is obtained are:

Voluntary notification.—Simple notification forms with minimum entries essential for our purpose are printed and distributed to all hospitals and physicians in private practice. Complicated forms may discourage cooperation; even with our simple form, the response has been discouraging.

The Medical and Health Department Institute of Radiology and Oncology.—This Institute, based at

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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[3] I thank Dr. the Hon. G. H. Choa, C.B.E., Director of Medical and Health Services, Hong Kong, for his permission to publish this paper; Messrs. K. Fung, H. K. Tam, T. Leung for data collection; and Mr. K. W. Leung for photographic assistance.

Queen Elizabeth and Queen Mary Hospitals, notifies us of over 2,000 new cancer cases each year. The Institute treats more than 80% of the patients referred for radiation therapy in Hong Kong; since the Registry is operated by the Institute, the most complete information is obtained from this source. Most patients attend the Institute mainly for radiation therapy, but about 10% receive chemotherapy.

Private hospitals.—Two private hospitals, the Hong Kong Sanatorium and the Hong Kong Central Hospital, provide the radiation therapy for the remaining 20% of the patients who require this service. In charge of each hospital radiation therapy department is a radiation oncologist who was formerly a member of the staff of the Medical and Health Department Institute of Radiology and Oncology. Each sends cancer data to the Registry regularly.

More than half the cancer surgery in the private sector is performed at these two hospitals. The Registry has access to patient records through the cooperation of the two radiation oncologists.

Government general hospitals —All cancer surgery, excluding that for bronchial cancer, performed in Government hospitals is done at Queen Mary and Queen Elizabeth Hospitals, which normally have 1,150 and 1,898 beds, respectively. Queen Mary is the teaching hospital of the University of Hong Kong. We have been fortunate in getting complete cooperation from the University's Professorial Surgical and Gynecological Units in notifying us of their cases. Additionally, all histopathologic investigations from all the clinical units of the University are conducted by the University Department of Pathology. The Professor of Pathology allows our Registry staff access to his departmental register of all histopathologic examinations. Thus at least one possible way that cancer cases diagnosed by other units could escape registration is eliminated. Those diagnosed without histopathologic examination here or at the University Department of Pathology will continue to be overlooked, but their number is limited. At Queen Elizabeth Hospital, the Registry staff regularly collects information from the patients' records and from reports of the pathology department of discharged cancer patients or of those who died in the hospital.

Hospitals for thoracic diseases.—The Grantham and the Ruttonjee Sanatorium on Hong Kong Island and the Kowloon Hospital in Kowloon admit patients with thoracic problems only. All lung cancer patients requiring surgery are referred here by the medical staff of the University or Government. The few patients who have surgery elsewhere mainly go to the Hong Kong Sanatorium, a private general hospital. The Registry obtains regular notification from all four hospitals; hence patients with lung cancer who have had surgery are well covered.

Government-subvented general hospitals.—Practically all cancer surgery in these hospitals is performed at the Tung Wah Group of three hospitals, with a total capacity of 7,868 beds. Some surgery is also done at the United Christian Hospital (545 beds), Nethersole Hospital (350 beds), and Lady of Maryknoll Hospital (262 beds). All but the Nethersole routinely notify the Registry of their cancer cases.

Pediatric Tumor Study Group.—This group, formed in 1973, collects and reports as much information as possible on patients from birth to 14 years who suffer from cancer, as diagnosed at Queen Mary and Queen Elizabeth Hospitals. At least 80% of all pediatric tumor cases diagnosed in Hong Kong are treated at these hospitals.

Hospital for cancer patients.—The Hong Kong Anti-Cancer Society operates the 120-bed Nam Long Hospital for terminal care, convalescence, or chemotherapy. This hospital regularly notifies the Registry of the case records of all its patients.

REGISTRATION COVERAGE

Coverage is estimated to be in excess of 80% for cancers of 1) the nasopharynx, which are treated mainly by radiation therapy; 2) the uterine cervix, also treated primarily by radiation therapy; 3) the trachea, bronchus, and lung; and 4) those of the esophagus, stomach, oropharynx, hypopharynx, and larynx. Highly sophisticated major surgery is required for the operable cases of cancer of the esophagus. Only the Queen Mary and Queen Elizabeth Hospitals and the Hong Kong Sanatorium have the necessary trained medical personnel and facilities for such surgery. Therefore, patients are referred first to surgeons in these hospitals, although some patients with esophageal cancer may be referred directly to radiation oncologists, through whom they are placed on the Registry. Surgery for operable cases of bronchial carcinoma would be performed at the specialty institutions or the Hong Kong Sanatorium. Inoperable cases would be referred to the Medical and Health Department Institute of Radiology or Oncology, the Hong Kong Sanatorium, or Hong Kong Central Hospital for radiation therapy or chemotherapy. Few patients are treated outside these institutions. Cancers of the

oropharynx, hypopharynx, and larynx are usually treated by radiation therapy first because most patients are reluctant to part with their larynx. If radiation therapy fails, patients normally are referred to the Professorial Surgical Unit at Queen Mary, where most of the head and neck cancer surgery is performed.

In summary, patients with childhood tumors or cancers that are treated predominantly by radiation therapy or by highly sophisticated major surgery would be registered. Our problem is registering those with cancers that do not belong in these categories.

Regrettably, a small percentage of patients will never come forward for treatment by practitioners of Western medicine and will rely to the end on traditional Chinese methods. These patients will not be registered; however, their number is decreasing gradually because of the successful cancer education program of the Hong Kong Anti-Cancer Society.

Other patients are afraid of the mutilating effects of surgery or the skin blemish caused by radiation therapy. With the introduction of megavoltage radiation and its skin-sparing effect, patients are now less afraid of subjecting themselves to radiation therapy. Some untapped sources of information are records of patients who have had histopathologic examinations performed by pathologists in private practice or in private hospitals; these records could be obtained from the pathologists concerned. Doctors sending them specimens for examination do not object to such access, since all personal data are kept strictly confidential within the Registry. Doctors usually object to filling in the notification forms because it is time consuming; they are indeed busy with their work. The Registry is now studying this problem.

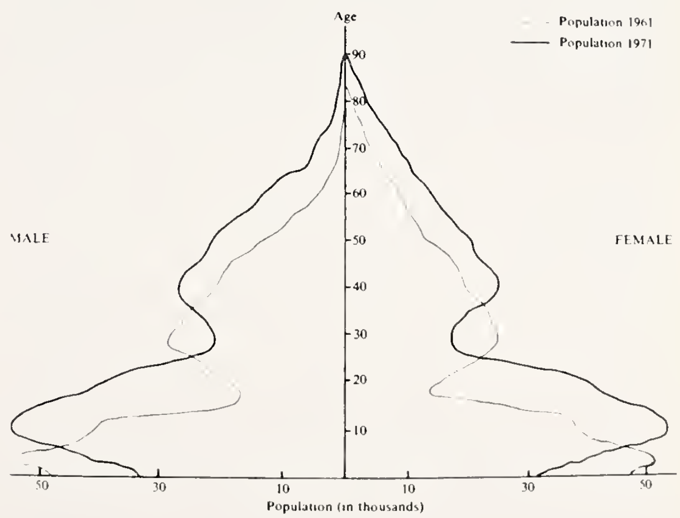
The Government Registry of Births and Deaths is another source that the Registry can use to broaden registration coverage and check final diagnoses of registered cases; access should not be difficult.

It is highly desirable to broaden the present coverage and scope of the Registry, but with our existing staff, we cannot plan much more. In 1969, we registered 5,308 new cases (2,739 males and 2,569 females). The number of certified deaths due to cancer was 3,839 (2,170 males and 1,669 females). The ratio of new cases to the number of deaths due to cancer was approximately 1.4:1; the registration rate was 133 per 100,000 population. This rate is about the same as that for Jews born in Asia or Africa, as reported by the Cancer Registry of Israel for 1960–66 (*1*).

Text-figure 1 shows the age pyramids of the Hong Kong population according to the 1961 and 1971 censuses. Compared with Occidental populations, our annual cancer incidence rate according to our Registry figures is low (less than half that of rates reported by most registries in Europe and the United States), but this could be explained partially by the fact that more than 50% of our population is below the age of 25.

Table 1 gives the numbers of new cases and deaths registered for the 7 most common cancers in Hong Kong during 1965–69. Although many new cases of primary malignant neoplasms of the liver and stomach have not been registered, the records of those of the trachea, bronchus, and lung are probably nearly complete because their salvage rate is low. As expected, the registration rate for cancers of the nasopharynx, uterine cervix, esophagus, and breast were high, probably close to 100%.

Histopathologic verification by reliable pathologists was obtained in well over 90% of most cancer cases, the exceptions being those of the liver and lung. Sputum cytology available in recent years has provided a means to verify the clinical and radiologic diagnoses in patients with disease too advanced for surgery or for whom bronchoscopic biopsies were either unsuccessful or contraindicated.



TEXT-FIGURE 1.—Age pyramids, Hong Kong, 1961 and 1971. Chinese constitute 98.4% of the population, and Chinese of Kwangtung origin constitute 92.6% of the Chinese population (Hong Kong Census and Statistics Department, 1972).

TABLE 1.—*Comparison of new cancer cases registered and certified deaths due to cancer in Hong Kong during 1965–69*

Primary malignant neoplasm	Cancer Registry	Death Registry
Trachea, bronchus, and lung	2,486[a]	2,486[b]
Nasopharynx	2,906	1,710
Stomach	1,532	1,814
Esophagus	951	782
Uterine cervix	2,823	742
Breast	1,767	686
Liver	1,834	2,326

[a] This number includes 1,520 males and 966 females.
[b] This number includes 1,454 males and 1,032 females.

TABLE 2.—*Incidence rates/100,000/annum of 7 most common cancers in Hong Kong, 1965–69*

Primary malignant neoplasm	Male		Female	
	Crude	Age-standardized	Crude	Age-standardized
Trachea, bronchus, and lung	15.57	27.95	10.26	12.75
Nasopharynx	20.28	24.30	9.29	10.20
Stomach	9.63	16.96	6.28	7.77
Esophagus	7.10	12.39	2.74	3.31
Uterine cervix	—	—	29.98	33.40
Breast	0.10	0.13	18.66	21.49
Liver	14.63	21.39	4.31	5.09

POPULATION-BASED STUDIES

The Government Department of Census and Statistics has taken a census of Hong Kong every 10 years since 1921, with a three-decade break between 1931 and 1961 as a result of the war. A bi-census was also taken in 1966. From the 1971 census, 20 million items of information were derived, many of which were useful for population-based studies (*2*).

Table 2 shows the crude and age-standardized incidence rates adjusted to the "world" standard population for the 7 most common cancers in Hong Kong for the period 1965–69 (*1*). In men, primary malignant neoplasms of trachea, bronchus, and lung have the highest age-standardized rate, but their crude rate is lower than that for cancers of the nasopharynx. Cancer of uterine cervix has the highest crude as well as age-standardized rate in females. The male to female crude incidence ratio in primary malignant neoplasms of trachea, bronchus, and lung is approximately 1.5:1; the age-standardized sex ratio is approximately 2.2:1. This ratio is low compared with those in Europe and the United States. Chinese women, particularly those of Cantonese origin, appear to have a much higher risk for lung cancer than Occidental women. Currently, these findings are the subject of a study as is the epidemiology of nasopharyngeal carcinoma, a cancer afflicting southern Chinese far more frequently than other ethnic groups. The current status of the latter was reported by Ho (*3*).

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Current Status of Cancer Studies in the South Pacific[1]

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ABSTRACT—An analysis of cancer incidence and mortality data indicated that cancer has become one of the five leading causes of death in many of the republics and territories in the South Pacific. The most developed areas had rates that exceeded world averages for malignant neoplasms of the lung, breast, and cervix uteri. The two existing cancer registries are in Papua New Guinea and Fiji. These registries have documented a number of unusual patterns of cancer incidence that allow casual inferences to be made. Among these are the association of chewing betel nut and cancer of the mouth, and the finding of Burkitt's lymphoma in Papua New Guinea with the same epidemiologic features as in West Africa. These and a number of other unusual patterns of cancer occurrence underline the need and the special opportunities for cancer research in the South Pacific.—Natl Cancer Inst Monogr 47: 61–66, 1977.

The peoples of the South Pacific are experimenting upon themselves concerning the causes of cancer. They chew betel nut, smoke cigarettes, breathe heavy metal dusts, and in numerous other ways they are exposed to environmental carcinogens. Few investigations have been made into the effects of these experiments. This report draws together what currently is known about the relative frequency of occurrence and the sources of information concerning cancer in the South Pacific.

As shown in text-figure 1, the region we are discussing includes 19 different republics and territories on both sides of the equator. It is a vast, sparsely populated area containing thousands of small islands and hundreds of different linguistic and cultural groups of people. For convenience, the region is often divided into areas inhabited by people with similar ethnic characteristics: Micronesia in the northwest, Melanesia in the southwest, and Polynesia in the southeast.

The information presented was obtained through written requests for age-specific cancer incidence data, through review of annual medical reports of participating governments, and from visits to existing cancer registries.

Some characteristics of the countries involved are listed in table 1. The total population is less than 4.5 million, of whom more than half live in Papua New Guinea. Using the definition of an urban center as an area having a population concentration of 8,000 persons or more who are involved in the wage economy, we can say that approximately 20% of the total population is urbanized. On Guam, 90% of the population lives in urban centers, whereas in Papua New Guinea, only 10% do. The annual growth of the major urban centers ranges from 4 to 30%.

Another common feature of these countries and territories is the variety of ethnic groups. For example, Noumea includes a population that is 50% European, 20% Melanesian, 15% Asian, and 15% from other islands. Fiji has a population that is 45% native Fijian, 50% Indian, and 5% from other islands. When different ethnic groups live side by side, an unusual opportunity for the comparison of different illness risk factors is provided.

The patterns of disease are changing rapidly in the South Pacific. In a few countries, the major causes of death are still infectious diseases, mainly of childhood. However, in most areas, these diseases are being controlled, the mean life expectancy is increasing, and the chronic problems usually seen in industrialized countries are becoming common.

Cancer is one of these problems. Less than 15 years ago, some authors (*1*) stated that all natives of Polynesia and Melanesia had an unusually low incidence of carcinoma. At present, cancer is one of the five leading causes of death in 6 of 12 Pacific countries.

The estimated annual number of new cancer causes and crude mortality rates for many of the South Pacific countries and territories are shown in table 1. At best these figures should be viewed as minimal estimates; in at least half the areas, they were based on hospital statistics only. For eight areas, we calculated the 3-year average annual incidence rates by type of cancer, as shown in table 2. These rates were age-adjusted to the 1960 population of the United States.

Several areas had incidence rates lower than

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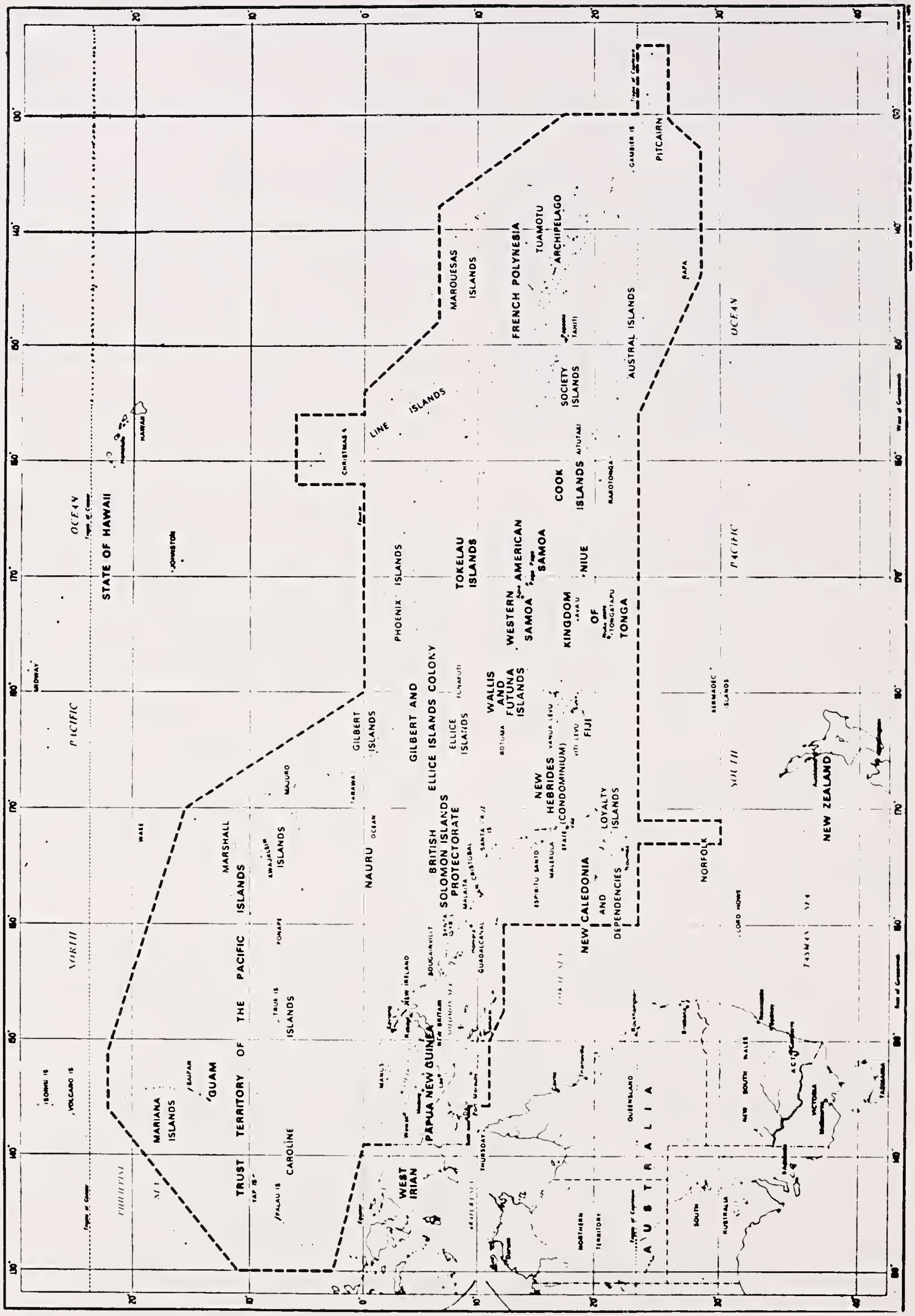

TEXT-FIGURE 1.—Map showing area of South Pacific Commission. Territories are within the South Pacific Commission area.

TABLE 1.—*Selected characteristics of the countries and territories of the South and Central Pacific*

Area	Estimated population	Percent urban	Percent indigenous	Mean life expectancy, yr	Estimated No. of new cancer cases/yr	Crude annual mortality rates for cancer[a]
Gilbert and Ellice Islands	57,000	29	99	51	45	13
Guam	105,000	90	55	63	370	51
Nauru	7,000	100	73	—	3	50
TTPI[b]	117,000	36	98	—	100	63
Micronesia subtotal	286,000				518	
Solomon Islands	179,000	10	99	57	230	
Fiji	551,500	34	46	60	200[c]	7
New Caledonia	126,000	59	55	55	400	44
New Hebrides	90,000	17	70	52	—	—
Norfolk Island	2,000	100	30	—	—	—
Papua New Guinea	2,625,000	10	82	43	1,500[c]	15
Melanesia subtotal	3,573,500				2,330	
Cook Islands	20,000	30	96	61	35	47
French Polynesia	128,000	57	74	58	65[c]	26
Niue	5,000	22	93	—	3	47
Pitcairn	100	—	90	—	0	—
Samoa, Western	152,000	21	99	62	224	
Samoa, American	30,000	42	98	66	17	64
Tokelau Islands	2,000	—	98	55	—	
Tonga	94,000	28	98	52	115	21
Wallis and Futuna Islands	9,000	—	98	—	—	—
Polynesia subtotal	440,100				459	
Total	4,299,600	20			3,307	

[a] Rates are calculated per 100,000 population.
[b] TTPI=Trust Territory of the Pacific Islands.
[c] Value includes only confirmed cases.

the median of some available worldwide rates (*2*). However, several countries had rates that exceeded known averages for several types of cancer (table 2). For example, Guam and New Caledonia exceeded known averages for leukemia and malignant neoplasms of the lung, breast, and cervix uteri. These two areas are the most developed of the South Pacific nations. The extremely traditional Cook Islands had high rates for cancer of the cervix uteri, liver, and oral cavity.

Table 3 gives the relative frequency in percentages of the 5 most commonly reported types of cancer for several areas. Nearly all countries frequently reported cancer of the uterus and breast, whereas over half of them included cancer of the gastrointestinal system, lungs, and skin. Oral and lymphatic cancers were the next most frequently reported types.

Cancer registries in this region are simple to describe, since only two are presently active. In Papua New Guinea, a registry was established by the Public Health Department in 1958. Its goal was to study the indigenous community and the types of cancers reported with particular reference to environmental influences. A recently published monograph describes the findings of this registry between 1958 and 1970 (*3*).

From the outset, it was recognized that complete coverage would be impossible and that results would have to be interpreted with due appreciation of the difficulties of investigations in a country unique in respect to social organization, communication difficulties, and limited medical services. For example, at least two-thirds of the population live in the seldom penetrated interior. More than 700 different languages are spoken; residents of villages only a few miles apart are often unable to understand one another. Demographic and vital statistics, the essential bases of medical research, are still in an elementary stage of development; the first census was completed in 1966. Most people have only a vague notion of their age. As late as 1971, only four hospitals had adequate diagnostic facilities for neoplastic diseases.

The cancer registry was based on two approaches, the first of which relied on notification from medical practitioners of all cancer cases encountered, either during medical patrol from village to village or at an administration or mission hospital. The registry form was completed, whether or not a pathologic specimen was available. The form also served as a request for histopathologic examination. The registry was

TABLE 2.—*Age-adjusted average annual incidence rates for cancer by area and type*

Causes (type of neoplasm)	Melanesia			Micronesia			Polynesia	
	Solomon Islands	Fiji	New Caledonia	Gilbert and Ellice	Guam	TTPI	American Samoa	Cook Islands
Buccal cavity, pharynx (ICD[a] 140–149)	11[b]	2	6	2	44[b]	11[b]	6	26[b]
Esophagus (ICD 150)	1	1	5	—	6		6	—
Stomach (ICD 151)	4	6	16	8	8		33[b]	22
Intestine except rectum (ICD 152, 153)	—	2	11	2	17	37	6	31[b]
Rectum and rectosigmoid junction (ICD 154)	2	2	9	—	7		3	—
Liver (ICD 155)	—	4	5	1	9[b]		1	16[b]
Larynx (ICD 161)	1	1	1	3	8	28	—	3
Trachea, bronchus, and lung (ICD 162)	—	6	31[b]	6	31[b]		11	5
Bone (ICD 170)	5	2	6	1[b]	6	22	—	2
Skin (ICD 172, 173)	18	4	18	6	46[b]		10	3
Breast (ICD 174)	12	17	35[b]	10	42[b]	16	39[b]	8
Cervix uteri (ICD 180)	4	22	43[b]	38[b]	42[b]	40[b]	19	116[b]
Other uterus (ICD 181, 182)	3	2	5	6	15[b]	6	7	32[b]
Prostate (ICD 185)	5	5	5	—	23	17	42[b]	36
Bladder (ICD 188)	—	1	2	—	5	—	—	14
Kidney (ICD 189)	—	1	3	—	3	—	—	3
Eye (ICD 190)	—	<1	1	—	—	—	—	—
Brain (ICD 191)	—	<1	1	1	1	—	—	—
Leukemia (ICD 204–207)	1	3	12[b]	1	16[b]	13[b]	9	3
Other lymphatic and hematopoietic tissue (ICD 200–203, 208, 209)	4	3	14	3	20	16	6	—
Other and unspecified sites (ICD 156–160, 163, 171, 183, 184, 186, 187, 192–199)	19	24	26	16	65	17	23	14
Benign or unspecified nature (ICD 210–239)	38	2	406	51	380	23	—	185
Total	117	93	677[b]	128	794[b]	226	168	427[b]

[a] ICD=International Classification of Diseases.
[b] This value exceeds world averages.

based at the Port Moresby General Hospital where all pathologic services were centered, and close liaison was established between the registry and the cancer centers in Australia. All reports without histopathologic verification were studied carefully and accepted only if the clinical and diagnostic evidence strongly supported a diagnosis of neoplastic disease.

In the second approach mortality surveys were used for continued observation of several village communities. The basis of the surveys was a recurrent semiannual census of selected village populations by European physicians. With the considerable under-reporting and variation from area to area, only large differences in relevant frequency or reported incidence could be used to draw reliable epidemiologic inferences. However, there was the hope that patterns of neoplastic disease would emerge and that they could be related to sociologic or environmental factors.

Despite many difficulties, this hope has been realized. Through this tumor registry, a number of unusual patterns of cancer have been demonstrated throughout Papua New Guinea, with significant variations in reported incidence or relative frequency to allow reliable inferences to be drawn from the data. Cases of cancer of the mouth were diagnosed 10 times more frequently in the coastal area where betel nut is chewed than in the highland areas where it is not. Another finding was that Burkitt's lymphoma occurred as frequently across Papua New Guinea as in West Africa and with the same clinical and epidemiologic features. Skin cancer, the second most commonly reported type, nearly always developed in the site of chronic tropical ulcers among Melanesians living in the coastal areas and in sites exposed to the sun among both Melanesians and Europeans living in the Highlands.

The only other functioning cancer registry in the South Pacific region was started in 1965 in Fiji, and a summary of the findings for the first 5

TABLE 3.—*Rank order of the 5 most commonly reported cancers by area and type*

Micronesia			Melanesia			Polynesia		
Islands or territories	No. of patients	Per-cent	Islands or territories	No. of patients	Per-cent	Islands or territories	No. of patients	Per-cent
TTPI (1970–73)	310		Papua New Guinea Cancer Registry (1958–70)	4,022		American Samoa (1971–73)	57	
Male								
Digestive		24	Male			Breast		13
Respiratory		17	Oral		18.4	Prostate		12
Bone and skin		11	Skin		17.4	Uterus		8
Lymphatic		10	Liver		10.9	Skin		8
Genitourinary		9	Digestive		8.5	Stomach		8
Female			Lymphoma		7.5	French Polynesia (1970–73)	237	
Genitourinary		33	Female					
Digestive		10	Genital		26.2	Skin		20
Respiratory		9	Skin		11.2	Female genitalia		11
Bone and skin		8	Breast		10.9	Lymphatic		11
Breast		6	Oral		10.0	Oral		11
Gilbert and Ellice Islands (1968–73)	227		Digestive		4.7	Breast		11
			New Caledonia (1971–73)	388		Tonga (1978)	59	
Uterus		15	Lung		12	Prostate		10
Skin		5	Uterus		11	Liver		10
Breast		5	Breast		8	Breast		5
Lung		5	Skin		7	Lungs		5
Oral		5	Lymphatic		7	Uterus		5
Guam (1972–73)	728		Fiji (1965–69)	1,042		Cook Islands (1970–73)	145	
Uterus		6	Cervix uteri		15	Uterus		8
Lymphatic		5	Breast		6	Intestine		6
Skin		5	Thyroid		4	Oral		5
Oral		4	Stomach		3	Stomach		4
Breast		4	Liver		3	Breast		3

years recently was published (*4*). The system is based on a two-stage notification scheme: preliminary notification of suspected cancer and a follow-up report on completion of the investigation. Although Fiji is much more developed than Papua New Guinea, a number of problems still affect the level of case ascertainment. About half the population lives on the main island of Viti Levu; the other half is scattered among 100 other small islands. People are often treated at local health centers and do not get to one of the three hospital centers where pathologic diagnoses can be made.

One of the most interesting aspects of a cancer registry in Fiji is that two very different ethnic groups live side by side. Between 1879 and 1916, over 40,000 Indians were brought to Fiji as indentured laborers. This group presently represents 50% of the population; the native Fijians, 45%. Each group maintains its social customs, diets, and traditions; intermarriage has been negligible.

During the first 5 years of recording, the incidence of all cancers was similar for these two groups. However, some unusual patterns were noted. The incidence of thyroid cancer was similar to that recorded in most other parts of the world for Indian men and women and Fijian men. For Fijian women, the rates were among the highest reported in the world. Primary liver cancer was similar to worldwide rates for Indian men and women and Fijian women, but several times higher among Fijian men. On the other hand, some cancers that are common in industrialized nations were rare in both ethnic groups in Fiji; these included cancers of the lung, stomach, colon, and rectum.

One other interesting finding from this registry concerns carcinoma of the cervix. As late as 1966, medical researchers have suggested that this type was rare among Fijian but common among Indian women (*1*). These reports were used by the advocates of male circumcision for cancer prevention since the majority of Fijian males practice circumcision, although most Indians (Hindu) do not. However, by 1971, 224 cases of cervical cancer had been registered in Fiji. One hundred and nine patients were Fijians and 98 were Indians; the other 7 were of various races.

One other cancer registry was started in Guam in 1971 but was dropped because of lack of funds. As all discharge diagnoses from Guam Memorial Hospital have been put onto computer tapes, it would be a simple matter to reestablish a registry for this Territory.

The general patterns shown in the two active cancer registries and in the available reports of cancer incidence for other areas follow the lines of the registries of other developing countries. Initially, a high proportion of reported cancers

reflects only those that are accessible. As the quality of medical service improves, the frequency of reported cancers increases and, ultimately, the true proportion becomes clear.

With an awareness of the limitations of these data, unusual patterns of cancer in the South Pacific still exist. These help us to understand the epidemiology of cancer and deserve more attention. Cancer will soon become a leading cause of mortality in the South Pacific. Because infectious diseases are now being controlled, people survive longer; and as uncontrolled urbanization increases, numerous changes will involve exposure to known carcinogenic agents. Therefore, this is the time to develop an ecologic approach to the investigations of this emerging problem in the South Pacific.

Certainly, one of the first steps is to establish cancer registries in many of the areas with accessible populations and to link these to an areawide system. Such a system was discussed at the 1976 Conference of Directors of Health sponsored by the South Pacific Commission.

Meanwhile investigations of known unusual patterns of cancer incidence could proceed independently. The high rates of lung cancer and leukemia in Guam and the Trust Territory of the Pacific Islands, liver cancer in the Cook Islands and Tonga, oral cancer in several territories, and Burkitt's tumor in Papua New Guinea, reflect problems that should be studied in greater detail.

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Epidemiologic Cancer Research Programs of the Cancer Center of Hawaii[1]

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ABSTRACT—Ongoing epidemiologic cancer research programs are described. These programs were developed by the Epidemiology and Demography Unit, Cancer Center of Hawaii, established in July 1974. During the 15-month period prior to the Pacific Basin Conference, many epidemiologic projects were initiated. Major descriptive, epidemiologic studies were undertaken: a) cancer mortality among the Japanese in Hawaii, adjusted by prefecture-of-origin; b) time trend of mortality rates for 80 causes between 1910–70; c) evaluation of race classification in Hawaii; d) survival analysis; and e) increased lung cancer rates among Japanese migrants in relation to smoking. Major analytic, epidemiologic studies were as follows: a) an international case-control study on breast cancer in relation to diet and exogenous estrogens; b) association between height and weight and various types of cancer; c) a follow-up study of about 9,000 shipyard workers exposed to asbestos; d) an epidemiologic survey on a 2- to 3-% sample population of Hawaii; and e) a follow-up study on leprosy patients in relation to their risks for cancer.—Natl Cancer Inst Monogr 47: 67–70, 1977.

Hawaii is comprised of migrant populations of different ethnic origins who vary greatly in their risks for many types of cancer. Thus Hawaii is a unique "human laboratory" and provides an unusual opportunity for epidemiologic cancer research. The Epidemiology and Demography Program develops cancer research projects that take advantage of these human resources in Hawaii. The geographic isolation and manageable size of the population offer another advantage for epidemiologic surveillance programs.

The first objective of the Epidemiology and Demography Unit (EDU) is to help improve the quality of cancer mortality and cancer incidence statistics, to assist in survival analyses, and to elucidate hypotheses that may explain the observed differences in cancer rates among various segments of Hawaii's population. The second objective is to develop epidemiologic cancer research programs to test these hypotheses.

The Cancer Center of Hawaii (CCH) was established in July 1974 through the support of a Cancer Center Grant from the National Cancer Institute (NCI). Although the EDU of the CCH has a short history, a number of projects have already been initiated. The following data give a progress report of these ongoing projects.

DESCRIPTIVE STUDIES

Cancer Mortality Adjusted by Prefecture-of-Origin

Remarkable differences are seen in the geographic distribution by prefecture (a self-governing unit) of cancer mortality rates in Japan. For example, gastric cancer mortality rates by prefecture range from 50 to 140% of the national average. Because Japanese migrants to Hawaii originated mainly from 5 of the 46 prefectures in Japan, comparisons between the national rates for Japan and those for Hawaii could be misleading. Therefore, cancer mortality ratios in these five prefectures, adjusted for frequency of migration, have been computed for better comparison with those for the Japanese living in Hawaii. Substantial deviations in the ratios from the Japanese national rate have been noted for certain types of cancer. Esophageal cancer for males, cancer of the buccal cavity and pharynx for both males and females, and cancer of the uterus showed much higher ratios than the national average. However, lower ratios for stomach cancers in males and females were observed. The results of this study will be published elsewhere (*1*).

Time Trend of Mortality Rates for 80 Causes Between 1910–70

In cooperation with the Hawaii Department of Health, mortality rates specific for race (white, Japanese, Chinese, Hawaiian, Filipino), sex, 5- or 10-year age groups, and 80 selected causes were computed for every census year in Hawaii between 1910 and 1970. Mortality rates for each census year were in fact annual average mortality rates for the 5-year period centering on the census year. Because of changes in International Classification of Diseases code numbers during these years, every death was recoded by computer

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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or by hand with the use of new code numbers that were assigned to those causes selected for this study.

The analysis is still in progress, but a preliminary tabulation of mortality rates has been completed. More than 1,000 tables have been produced from this study; these will be further analyzed and the results published.

Race Classification

Accurate and consistent race classification is essential for comparison of cancer rates in different races and different time periods in Hawaii. The EDU tries to evaluate the consistency of the race classification system of Hawaii.

In our current negotiations with the United States Census Bureau regarding a comparability study of racial designation between census accounts and death certificates, we proposed that we provide a list of deceased persons, classified by race, based on death certificates reported within the 6-month periods immediately after the 1960 and 1970 Censuses. These persons would be reclassified by race by the Bureau, based on the census survey. We have been cautioned that such a request could be time-consuming and expensive because matching can only be done by hand. However, since this is the best method for comparing racial designations in the numerator and denominator of death rates, we hope this proposed project will materialize.

Survival Analysis

Since the Tumor Registry of Hawaii was established in 1960, a large number of reported cancer cases have been accumulated. Survival status is known for most of these cancer cases. The Tumor Registry of Hawaii and the EDU have initiated a survival analysis study for all major cancer sites by race, sex, and stage of cancer.

In addition to analyzing data on patients whose survival status is already known, we are making special efforts to trace lost-to-follow-up cases so survival status can be ascertained for more than 90 to 95% of the patients. At present, we are focusing on cancer of the colon, rectum, and breast, and we now have traced 96% of the former (as of the selected common closing date of December 31, 1973). Survival status of patients with cancers of the colon and rectum is being analyzed in terms of crude survival rates with the life-table method, relative survival rates with standard errors, and chi-square values (*2*).

Increased Lung Cancer Rates Among Japanese in Hawaii in Relation to Smoking

The lung cancer mortality rate for Japanese in Hawaii nearly equals that for United States whites, whereas the rate for indigenous Japanese is much lower (one-third the rate for United States whites). We do not know whether these variations can be explained by differences in smoking habits between the two Japanese populations.

Through the cooperation of the Honolulu Heart Study and the Atomic Bomb Casualty Commission (currently known as the Radiation Effects Research Institute), we obtained punchcards bearing smoking information for approximately 8,000 Japanese men living in Hawaii and 2,600 men in Hiroshima and Nagasaki. Analysis of these data is in progress (*3*).

CASE-CONTROL STUDIES

Through a grant from the Breast Cancer Task Force of NCI, we are investigating the possible associations of breast cancer with noncontraceptive estrogen intake and diet (animal protein and total fat). The study design entails a comparison of breast cancer cases, with neighborhood and hospital controls in populations differing greatly in their risks for breast cancer: Caucasians in Hawaii, Japanese-Americans in Hawaii, and indigenous Japanese in Fukuoka, Japan. A detailed description of this study appears elsewhere in this monograph (p 165).

COHORT STUDIES

De Waard and his co-worker (*4*) of The Netherlands have reported that overweight and tall women are at a higher risk of developing breast cancer. We are studying this association between breast cancer and height and weight by utilizing the Civil Defense File containing data on about 300,000 Hawaii residents in 1942. This information has been stored on computer tape in the Data and Computation Unit of the CCH.

The Civil Defense file has been linked with the Death Certificate file of Hawaii. For the period between 1950–70, 209 deaths from breast cancer have been identified in this cohort. The preliminary analysis of these data indicates that postmenopausal women with breast cancer tend to be heavier and taller than the average for the Civil Defense Survey population of comparable race and age.

A Follow-Up Study of Workers at the Pearl Harbor Naval Shipyard

A follow-up study of workers at the Pearl Harbor Naval Shipyard with varying levels of asbestos exposure is being conducted by EDU. A retrospective cohort of about 9,500 male shipyard workers, on the rolls in 1950 and employed subsequently through 1970, has been identified. Various trades at the shipyard have been categorized into 3 groups in terms of exposure to asbestos. We completed an 80% follow-up and intended to trace more than 95% of the workers through January 1974. Tracing of this cohort has involved other mainland shipyards, the Driver's License Bureau of the Hawaii Police Department, Medicare, social welfare agencies, the State Income Tax office, and the use of Polk's City and Island directories for Hawaii.

When the follow-up has been completed, mortality in this cohort by exposure category will be compared with expected mortality, which will be computed from the mortality experience of the Hawaii population of comparable sex, age, and race. Tests of significance and relative risks will be computed for all causes of death, noncancerous pulmonary diseases, all cancer, and site-specific cancers. As of November 1975, more than 600 deaths have been uncovered in this retrospective cohort.

In addition to mortality analyses for the time period between 1950 and 1974, those workers identified in 1974–75 as being alive and residing in Hawaii will be followed prospectively; we intend to determine:

1) cancer incidence by site through the Hawaii Tumor Registry,

2) interaction effect between smoking and asbestos exposure based on smoking history data obtained from the workers,

3) pathologic confirmation of the diagnoses of methothelioma and bronchogenic carcinoma, and

4) the degree of asbestos exposure in different trades in the shipyard.

Epidemiologic Survey on Hawaii Residents

We are interested in acquiring data on smoking, drinking, and dietary habits from a representative sample of Hawaii's multiracial population for our studies on ethnic–racial differences in cancer incidence in Hawaii. Since 1969, the Hawaii Department of Health conducted a continuous Health Survey on a 2- to 3-% representative sample of the State's population. This survey covers all major islands and yields about 6,000 households annually. The interview form in current use includes several health-related items and a number of demographic items of epidemiologic interest. However, it does not include dietary and smoking information.

We developed a concise questionnaire on dietary, drinking, and smoking habits that has been incorporated into the Health Survey Questionnaire. Only food items of suspected or potential etiologic importance in cancer have been included. This epidemiologic survey will be conducted for a 5-year period and will yield data on a sample of about 60,000 persons.

Before the final form of the questionnaire was settled, it was pretested on nearly 100 individuals by interviewers on our staff. In addition, a quality control study is being conducted on 300 married couples to test whether a wife's statements about her husband's habits coincide with those stated by the husband himself. This is necessary because many of the husbands are away from the home at the time of the regular interview.

The epidemiologic survey has two purposes: 1) Possible associations between cancer risks and the information on diet, smoking, and drinking habits can be investigated in different ethnic groups. For example, the unusually high risk for lung cancer observed among males in the Hawaiian ethnic group may be associated with possible excessive cigarette smoking among the Hawaiians. 2) The study also hopes to follow the cohort of about 60,000 men and women after the interview and to correlate later occurrences of cancer with their present diet, smoking, and drinking habits.

Leprosy Patients and Cancer

One theory of carcinogenesis of current research and clinical interest maintains that the development of tumors represents a breakdown in the body's normal immunosurveillance mechanism, whereby abnormal cells are routinely destroyed. Leprosy patients represent an interesting population for study in this regard. Patients with the lepromatous form of leprosy appear to have depressed cell-mediated immunity, whereas those with the tuberculoid form manifest no such deficiency. Thus one might expect an increased incidence of tumors among the former group and a normal or even reduced incidence among the latter.

Hawaii has been one of the endemic foci for leprosy in the United States. We initiated a follow-up study on persons with leprosy with the cooperation of the Leprosy Branch of the Department

of Health and have identified a cohort of more than 1,300 patients. They are being traced by various means, and their cancer mortality will be compared with expected numbers based on the mortality rates of the general population of Hawaii for comparable race, sex, and age groups during the corresponding calendar years (5).

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Cancer Registry in Chile: The Situation in Developing Countries [1]

Rolando Armijo, *M.D., M.P.H.* [2]

ABSTRACT—In Chile, the first population-based cancer registry was established in 1958 and later became part of the overall statistical system. At present, only limited data are being collected. Other Latin and South American countries developed their registries with the support of the Pan American Health Organization. However, growth of registries in developing countries must be commensurate with evolution of data-recording systems in other sectors. A study ranked Chile second in the world regarding age-adjusted mortality rates from stomach cancer. Analysis of death rates among its 25 provinces for a 15-year period (1957–71) showed a peculiar geographic pattern of high- and low-risk areas. Three agricultural provinces had a median rate of 50.1/100,000. In contrast, less than half the risk is observed in the extreme northern and southern regions of the country; three northern provinces had a median rate of 21.6, whereas in the extreme south, it was 22.8. Data showing the use of nitrates were collected for the period 1945–72. A high correlation was found between death rates and cumulative per capita exposure to nitrogen fertilizers. Controlling for confounding socioeconomic variables, the correlation held at a significant level. This study would not have been possible without data supporting the evidence presented.—Natl Cancer Inst Monogr 47: 71–75, 1977.

The history of cancer registries in Chile and other countries in Latin America is a short one; not a great deal can be reported on this subject. In Chile, the first registry was established in 1958 by Dr. Juan Moroder, a distinguished Spanish epidemiologist. He died shortly thereafter (in the early sixties), and the registry then became part of the overall system of health statistics maintained by the National Health Service. Since then, it was possible to calculate incidence rates for cancer for males and females; the high incidences of stomach cancer in both sexes and of cancer of the uterine cervix in women are significant findings.

The registry includes data from the whole country (population: 10 million), but the quality and completeness of the information has varied. The city of Valdivia has a regional registry that collects data from 10 of the 25 provinces in Chile. This registry is more like a hospital tumor registry than that of a population-based one. In Santiago, the Catholic University Hospital maintains a registry of bone tumors, whereas one children's hospital maintains a special one of childhood tumors. Other than these registries and the general health statistical data (which traditionally have been reliable), no population-based nationwide registry exists. We have a National Cancer Commission that is responsible for cancer surveillance.

In 1969 in Colombia, the Pan American Health Organization sponsored a Seminar on Cancer Registries in Latin America (*1*) with Roy M. Acheson, John C. Bailar III, Sidney J. Cutler, Isidro Martinez, Abraham Ringel, and Calvin Zippin as consultants. This meeting laid the foundation for the development of registries in several countries, operating at different levels and with a wide variety of coverage.

Growth of registries in all developing countries must be commensurate with the evolution of data-recording systems existing in other sectors and particularly in health statistics. In other words, the cancer registry cannot be better than other data systems, and no effort should be made to improve the registries alone if grounds 1) to support cancer data, 2) to study any possible associations, or 3) to test hypotheses are unavailable. To illustrate this point, I will summarize some of the highlights of a study on the epidemiology of stomach cancer and the use of relevant data.

STOMACH CANCER IN CHILE

Chile ranks second in the world in age-adjusted mortality rates from stomach cancer for males and females (*2*); this accounts for 30% of deaths from malignant neoplasms (*3*). Table 1 summarizes the death rates for the years 1957 through 1971. The median, minimum, and maximum values found for this 15-year period coincide. Three agricultural provinces (Maule, Linares, and Ñuble), comprising a population of 460,000 in 1971, consistently have the highest values, with a median death rate of 50.1/100,000. These provinces are located south of Santiago, the capital city. In contrast, both extremes of the country, spanning approximately 3,000 miles, experience a risk of less than one-half. The three northern

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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TABLE 1.—*Stomach cancer mortality per province, Chile, 1957–71 and age-adjusted mortality rates for 1960*

Province	Death rates from North to South, 1957–71			1960	
	Minimum	Median	Maximum	Population	Age-adjusted rates
Tarapacá	14.2	21.3	30.6	123,070	25.4
Antofagasta	15.6	20.6	27.6	215,219	26.9
Atacama	19.9	23.7	29.4	116,235	29.3
Coquimbo	29.4	35.4	40.9	308,991	38.1
Aconcagua	35.0	37.1	51.0	140,543	39.9
Valparaíso	28.8	38.0	47.7	617,510	46.6
Santiago	26.1	28.8	33.0	2,437,625	34.1
O'Higgins	31.7	38.2	41.1	259,470	40.7
Colchagua	32.3	42.9	55.9	158,509	55.0
Curico	32.8	44.2	62.4	105,802	56.5
Talca	28.7	39.6	60.5	206,154	69.6
Maule	38.5	51.8	80.0	79,736	47.9
Linares	32.7	48.3	61.3	171,350	44.6
Ñuble	40.6	50.8	56.5	285,639	61.8
Concepción	29.8	34.5	48.5	539,521	68.3
Arauco	24.2	34.5	51.9	89,460	35.6
Bío-Bío	23.2	39.0	48.6	168,718	49.3
Malleco	28.3	42.3	54.4	174,300	62.7
Cautín	28.3	35.1	54.4	394,654	46.1
Valdivia	22.4	27.9	37.0	259,794	33.6
Osorno	20.3	23.5	28.5	144,005	34.3
Llanquihue	16.5	23.7	35.3	167,671	33.0
Chilóe	14.4	32.5	53.5	99,211	26.5
Aysén	11.3	19.0	29.9	37,770	41.5
Magallanes	15.0	25.8	39.2	73,156	27.2
Total	30.1	33.8	36.4		

provinces (Tarapacá, Antofagasta, and Atacama), with a 1971 population of 652,500, have a median rate of 21.6/100,000, whereas both Aysén and Magallanes in the extreme south (population 161,600) have a median rate of 22.8.

HYPOTHESIS, ASSUMPTIONS, AND METHODS OF ANALYSIS

Our hypothesis was that death rates from stomach cancer in Chile correlated with the general population exposure to nitrates from either the drinking water or from the extensive use of nitrogen fertilizers. To test this hypothesis, we collected data from the following sources:

1) *National Health Service:* We acquired detailed data on the population, deaths, and death rates for stomach cancer for each of the 25 provinces for the years 1957 through 1972. Also, data were collected on infant mortality rates and death rates for other major cancer sites per province.

2) *The Chemical Society of Chile:* The use of sodium and potassium nitrates and synthetic nitrogen fertilizers, expressed in tons of nitrogen from 1945 until 1972, per province, was obtained from records prepared specifically for this study.

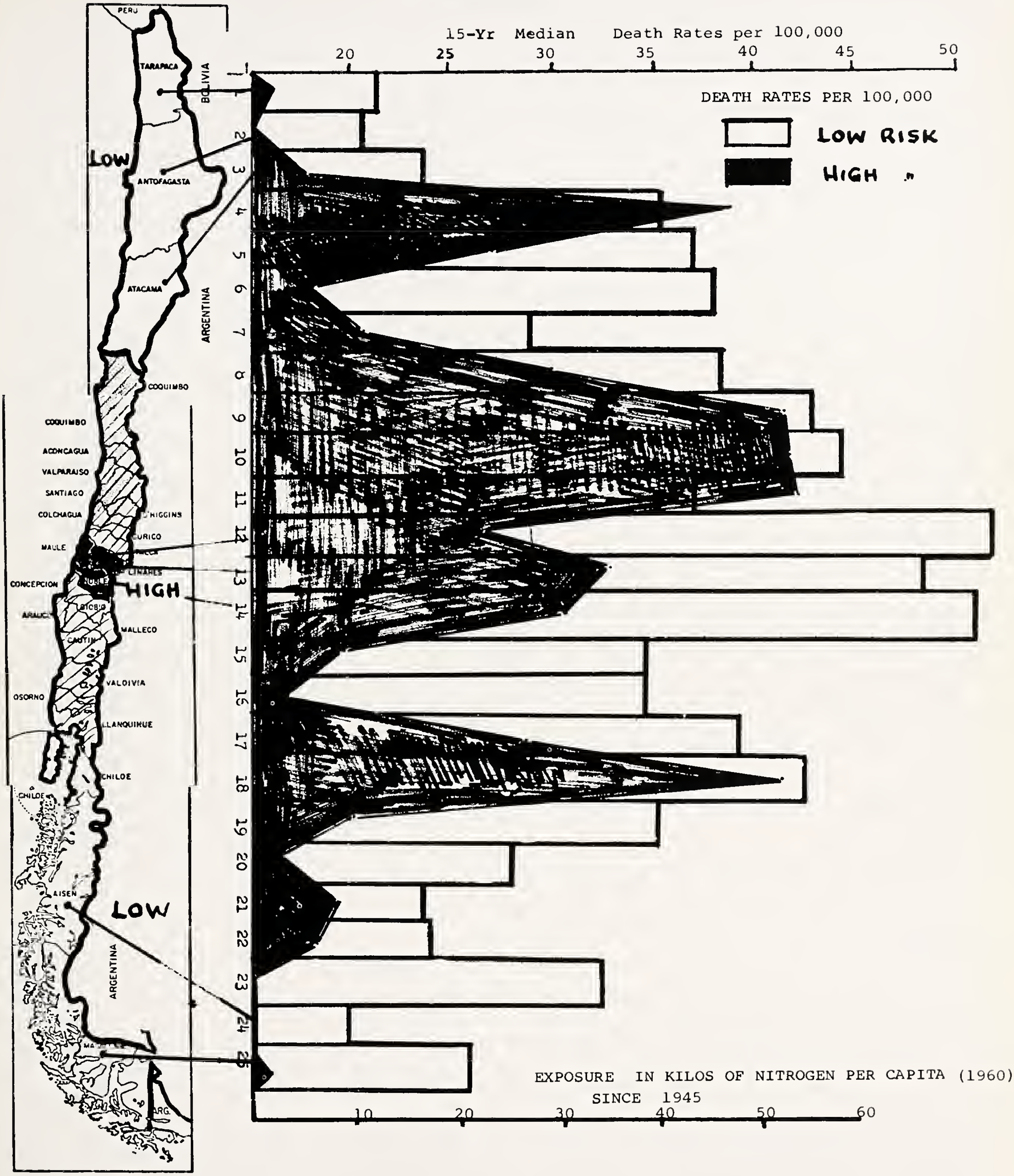
3) *Water Supplies Authority, Water Laboratory of the School of Public Health, University of Chile, and others:* Information on nitrate concentration in the drinking water throughout the country was provided.

The nitrate pattern in the drinking water as well as the distribution pattern for nitrogen fertilizers in the 25 provinces was studied. For the distribution pattern, a cumulative exposure expressed in kilograms per capita was calculated. The correlation between exposure and stomach cancer was explored by various methods for different periods of time. We tested other confounding variables that could have an impact, such as socioeconomic conditions, by using infant mortality rates and housing ratings as indicators. Other major cancer sites were also studied in comparison with stomach cancer.

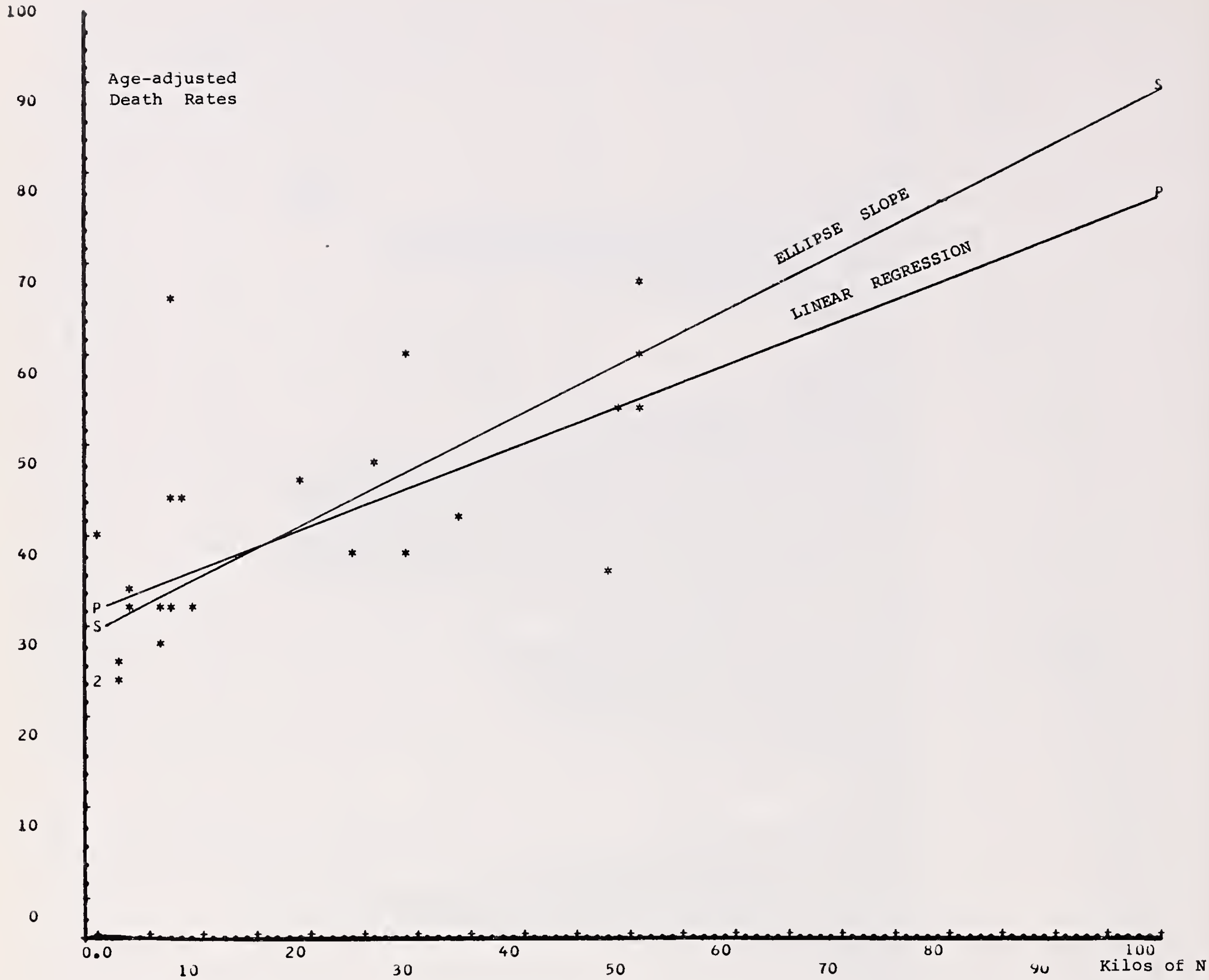
Chile is the only country in the world that produces natural nitrates (saltpeter). Traditionally, we have used sodium and potassium nitrates as fertilizers for a wide variety of crops, such as rice, beans, corn, wheat, potatoes, fruit trees, vineyards, and more than 20 fresh vegetables. Thus one can assume that the population is exposed to a high intake of nitrates, regardless of the diet. Nitrate concentrations ranging from 22.5 to 34.5 ppm in twelve samples of underground water in agricultural areas adjoining Santiago (significantly higher than the concentrations found in the drinking water) strongly suggest that there may be a concentration of nitrates throughout the water table.

Nitrates are produced in the northern provinces of Tarapacá and Antofagasta, then shipped and distributed throughout 20 agricultural provinces. The various crops, in turn, are shipped to the urban centers of Santiago, Valparaíso, Concepción, and others, as well as to the nonagricultural provinces in both extremes of the country, where the people consume less vegetables than those living in the central provinces, because the produce has to be imported from the center and, consequently, is more expensive.

Assuming that nitrogen goes into the various crops and into the water table, our next step was to find a suitable indicator for exposure because nitrogen reaches the population through numerous channels. However, the per capita cumulative exposure may be subject to several criticisms. For example, because the provinces are not isolated units, agricultural products are traded between them in different ways. Therefore, the possible association between nitrates and stomach cancer should plateau; however, if correlations are still found, their importance would be enhanced.



Text-figure 1.—Death rates from stomach cancer and exposure to nitrates, 1957–71 (median).



TEXT-FIGURE 2.—Stomach cancer mortality and per capita cumulative exposure to nitrogen by province, 1960.

CONCLUSIONS

The cumulative per capita exposure paralleled mortality trends, with exceptionally low nitrogen exposure noted at both ends of the country (text-fig. 1). High rates of nitrogen exposure, i.e., from 140 to 448 kg per capita, are observed in the central provinces. The regression of gastric cancer mortality on per capita nitrogen exposure by provinces (the correlation is 0.66) is illustrated in text-figure 2. Two regression lines are shown on the graph: The steeper slope represents the main diagonal of an ellipse describing the data, whereas the lesser slope represents the more common least-squares regression line. The ellipse slope is less affected by outlying values, and is preferable here, where a single year of mortality (1960 age-adjusted mortality) is used to represent the long-term experience (*4*).

When we made an adjustment for confounding socioeconomic variables, estimated by housing factors and infant mortality rates, the correlation was significant. A negative correlation between stomach cancer and infant mortality rates, low correlation with the rating assigned to housing, and a negative correlation with deaths from lung and cervical cancer were also found. This negative correlation reinforces the lack of association with socioeconomic conditions. However, other major sites show a completely different pattern. The

epidemiologic evidence presented agrees with biochemical findings on the synthesis of nitrosamines (*5, 6*).

It would have been impossible to do this study without data on 1) nitrate usage by province since 1945, 2) nitrate concentrations in the entire drinking water supply, 3) infant mortality rates, 4) other sites of cancer, 5) selected socioeconomic indicators such as the housing index, and 6) the population data categorized by provinces.

My own experience (internationally) strongly indicates that cancer epidemiologist–statistician specialists in their enthusiasm tend to overlook or disregard the other components of the health and socioeconomic picture that are of crucial importance for the interpretation of data on cancer incidence, mortality trends, etc. We do need to establish a stable foundation for the registration of cancer data, coordinating our efforts with those of parallel data-recording sectors to make maximum use of cancer information.

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Cancer and Chronic Disease Surveillance in British Columbia[1]

Richard P. Gallagher, *M.A.*[2,3]

ABSTRACT—The British Columbia Health Surveillance Registry recorded morbidity information on a number of chronic and disabling diseases. The Cancer Register, the largest within the agency, achieved good ascertainment of neoplasms within the Province. In 1973, a total of 8,397 new cancer cases, excluding cases of carcinoma in situ, were diagnosed and reported. The general register ascertained congenital anomalies and other physical and mental disabilities within British Columbia. At the end of 1971, approximately 20,111 anomalies had been recorded. The Record Linkage Program currently underway in British Columbia will eventually link records of cancer, congenital anomalies, live births, marriages, and other vital events on a continuing basis for research purposes.—Natl Cancer Inst Monogr 47: 77–80, 1977.

At the present time, British Columbia has several registers recording information on individuals with chronic or disabling diseases. These function under the overall title of the British Columbia Health Surveillance Registry.

The Registry's area of ascertainment includes the entire Province, an area of approximately 366,250 square miles. The population in 1974 was about 2.4 million, with the largest ethnic groups coming from the British Isles and western Europe. Native Indians comprise about 2.4% of the population and Orientals, 2.6%. The population of British Columbia is "older" than the average age of the rest of Canada.

One of the major entities within the Health Surveillance Registry is the Cancer Register, the staff of which collects and maintains information on all cases of malignant neoplasms diagnosed in the Province. Congenital anomalies, genetic defects, handicapping injuries and diseases, mental retardation, blindness, deafness, and many other disabilities also are reported to the Health Surveillance Registry. Information also is collected on mothers who undergo amniocenteses and on children whose mothers had rubellae during pregnancy.

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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In this paper the history, development, and present status of the surveillance system in British Columbia will be discussed, with particular reference to cancer notification. This will be followed by a brief description of the developing Record Linkage Program, which will link, by computer, the Health Surveillance Registry caseload with other vital and health documents.

THE CANCER REGISTER

History

In 1932, at the request of the British Columbia Medical Association, cancer was added to the list of diseases notifiable to the Provincial Government. The actual reporting system went into effect in 1935, at which time physicians were requested to notify the Department of Health of all malignant neoplasms diagnosed; a standard notification form was introduced.

Reporting by private physicians alone was not successful in achieving good ascertainment. Therefore, the Department of Health solicited notices from hospital record departments and the British Columbia Cancer Institute.

The cancer notification system was expanded in 1967 to become the Cancer Register. At that time, a file of known live cases was instituted with cancer notifications dating from 1963. A file of dead cases was instituted in 1969. Live and dead registers have been maintained to date. In 1969, arrangements were made for copies of pathology reports on cancer cases to be submitted to the Cancer Register. These reports are now the major source of ascertainment. The aims of the Cancer Register are: 1) to obtain incidence and prevalence figures for cancer in British Columbia, and 2) to maintain a central index of cases for the provision of statistical information on request.

Ascertainment and Cancer Register Procedures

The sources of ascertainment used by the British Columbia Cancer Register at present are: 1) reports from hospital pathology laboratories, 2) notifications from the Cancer Control Agency, the major treatment facility in the Province, 3) reports from provincial mental health services,

TABLE 1.—*Malignant neoplasms diagnosed and reported by site and sex, British Columbia, 1973* [a]

Site	ICDA rubric	No. of: Male	No. of: Female	No. of: Total	Incidence/100,000 population Male	Incidence/100,000 population Female	Incidence/100,000 population Total
Buccal cavity and pharynx	(140–149)	151	56	207	13.0	4.9	8.9
Digestive system	(150–159)	883	789	1,672	75.8	68.6	72.2
Respiratory system	(160–163)	709	183	892	60.9	15.9	38.5
Skin	(172–173)	1,171	952	2,123	100.5	82.8	91.7
Breast	(174)	4	918	922	–	79.8	79.8[b]
Female genital system	(180–184)	–	581	581	–	50.5	50.5[b]
Male genital system	(185–187)	596	–	596	51.2	–	51.2[b]
Urinary system	(188–189)	320	123	443	27.5	10.7	19.1
Eye, brain, and nervous system	(190–192)	68	53	121	5.8	4.6	5.2
Endocrine glands	(193–194)	15	50	65	1.3	4.3	2.8
Lymphatic and hematopoietic system	(200–209)	273	185	458	23.4	16.1	19.8
Other sites including secondary	(170–171) (195–199)	170	147	317	14.6	12.7	13.7
Total	(140–209)	4,360	4,037	8,397	374.2	351.0	362.7

[a] All cases of carcinoma in situ are excluded.
[b] Values are sex-specific rates.

4) notifications from private physicians, 5) autopsy reports, mainly from hospitals, and 6) death registrations.

Notifications of new cancers to the Cancer Register are checked against the current caseload to ensure that no duplication occurs. If ambiguities on site or histology appear or if adequate patient identification is lacking, the reporting physician is queried before the case is registered. A consultant pathologist advises on interpretation of pathology reports.

Anatomic site is coded according to the International Classifications of Diseases Adapted (ICDA) (*1*), and morphology according to the *Manual of Tumor Nomenclature and Coding* (*2*). Secondary sites to unknown primaries are coded by the Register but are discarded when information on the primary site becomes available.

Every month, a list of all deaths occurring in the Province is checked against the Register caseload. Deaths of registered patients and cases for which no notification has been previously received are recorded from these lists.

Registrations are transferred to punchcards, and two card decks are made up: a "notification" and a "register" deck. Essentially, a single notification card represents a single neoplasm, whereas a single register card represents a single individual with any number of neoplasms.

Current Status of the Data

At present, the diagnostic information recorded by the Cancer Register is confined to site and histology. Since the major component of notification consists of pathology reports, site and histology data are reliable. We are not recording now some patient identification data (such as birth surname and full date of birth) on the machine-readable punchcards. Mechanisms for acquiring this information in the future and for updating past files are being explored.

Ascertainment of cancer in British Columbia is virtually complete. Until recently, lack of reporting by hematology laboratories may have resulted in some underascertainment of leukemia.

In 1973, the Cancer Register recorded a total of 8,919 new malignant neoplasms, excluding cases of carcinoma in situ. Of these, 8,397 were diagnosed and reported in the year 1973 (*3*).

Figures from the Cancer Register are used to monitor incidence rates in various parts of the Province. The Cancer Control Agency uses Register figures to determine optimum geographic location for new facilities and cancer screening programs.

GENERAL REGISTER INCLUDING CONGENITAL ANOMALIES

History

In 1948, the Canadian Federal Government made available to the Provinces grants for the development of health services. In British Columbia, the grant was used to survey the number of children in the Province affected by chronic handicapping diseases. When the survey was completed in 1950, 20,000 cases had been ascertained. As a result, the Crippled Children's Registry was established. Registration was opened subsequently to adults and gradually was expanded to include certain special groups, such as children whose mothers had rubellae during pregnancy and mothers who had undergone amniocenteses. The

TABLE 2.—*Ascertained congenital anomalies of children, born live in British Columbia,[a] during 1952–71*

Diagnostic category	ICDA rubric	Male	Female	Total
Ear, eye, face, and nervous system	(740–745)	1,542	1,317	2,859
Cardiovascular system	(746–747)	2,233	2,044	4,277
Respiratory system	(748)	92	67	159
Cleft palate and lip	(749)	802	564	1,366
Digestive system	(750–751)	1,003	449	1,452
Genital organs	(752)	1,474	96	1,570
Urinary system	(753)	538	458	996
Musculoskeletal system	(754–756)	2,966	2,951	5,917
Anomalies of skin, hair, and nails	(757)	118	122	240
Other and unspecified anomalies excluding syndromes	(758)	50	34	84
Congenital syndromes affecting multiple systems	(759)	599	592	1,191
Total anomalies	(740–759)	11,417	8,694	20,111

[a] Values include anomalies of cases now dead.

evolution of this Registry was described in (*4*). Recently, it was decided that the name of the Registry should reflect the fact that many different types of conditions, including cancer, are recorded. Thus in 1975, the name became the British Columbia Health Surveillance Registry.

In 1952, medical services for the handicapped were poorly organized. Therefore, the goal of the Registry at that time was to ensure that handicapped children and their parents received appropriate rehabilitation, treatment, and counseling. As health services improved, this function was largely superseded. Today, its primary functions are to monitor the incidence of registrable diseases in the Province and to provide data for research on these conditions.

Procedures

For the general registers, a registrable person is "one who possesses a physical, mental or emotional problem which is likely to be permanently disabling, to interfere with his education, or to prevent full or open employment; also any person with a familial condition or congenital malformation . . ." (*5*).

Because reporting is not compulsory, multiple sources of ascertainment are used to compensate for this possible deficiency. They are: 1) physician's notice of birth, 2) Public Health Unit notifications, 3) reports from special treatment centers, 4) reports from voluntary health agencies, 5) death registrations, 6) stillbirth registrations, and 7) hospital admission–separation records of patients with congenital anomalies.

Disabilities are coded according to the ICDA (*1*). Additional codes are used to indicate causation, including genetic etiology; clinical, laboratory, and family history evidence supplied with a notification is used for determination of etiology. Consultants in genetics and pediatrics advise on the coding of difficult cases. Trimble and Doughty (*6*) found that about 9.4 individuals of every 100 live-born are affected at some time in their lives by a genetic disease or handicap.

Table 2 gives the numbers of some of the conditions ascertained to the end of 1971.

RECORD LINKAGE PROGRAM

In view of evidence that indicates the possible relationship between some malignant neoplasms and congenital anomalies (*7–9*), attempts are being made to collate information from all Registers in the Province.

A Record Linkage Program has been initiated by the Division of Vital Statistics in collaboration with the Department of Medical Genetics at the University of British Columbia. The program uses methodology developed at the Chalk River Nuclear Laboratories by Dr. H. B. Newcombe (*10*). When the program is fully functional, data from many sources will be linked on a continuing basis. Included will be records of live births, stillbirths, deaths, marriages, hospitalizations, congenital anomalies and other chronic diseases, and cancer.

A project is currently being developed to link the Cancer Register file with provincewide hospital admission–separation data. This will allow transfer of valuable identifying information to the cancer file, making it more versatile for research purposes.

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Possible Use of Short-Term Tests for Carcinogens in Experimental Epidemiology [1,2]

H. F. Stich, R. H. C. San, *and* P. Lam [3]

ABSTRACT—This brief overview pointed out the feasibility of applying the recently developed short-term bioassays for carcinogens/mutagens to the field of epidemiology. The simplicity and economy of these test systems permitted their adaptation for large-scale screening for intrinsic and extrinsic carcinogens with an eye to detecting subpopulations with elevated sensitivity to particular carcinogens.—Natl Cancer Inst Monogr 47: 81–85, 1977.

Studies in the cancer etiology of man are hampered by three phenomena: the long latent period before macroscopic or microscopic appearance and diagnosis of tumors; the vast number of compounds and mixtures of compounds inhaled, smoked, drunk, eaten, injected, or painted on skin, hair, nails, etc.; and the lack of information about the quantities of various chemicals actually consumed by persons of different countries, social levels, religious affiliations, and ethnic groups. New procedures are required to cope with this situation. Clinically detectable cancer is an end point that is too far removed from the original etiologic factors. To contend with the problem of long latency of tumorigenesis, new criteria must be sought that will provide information within a short time following exposure to carcinogens. The second issue, the detection of carcinogens in man's environment, cannot be approached if we rely exclusively on painting or feeding experiments of mice, rats, or hamsters. These "classical" methods are too time consuming (about 3 yr from the planning stage) and too expensive (in United States dollars, about $120,000 to $150,000/compound) to be applied in any large-scale screening program. Furthermore, they do not provide insight into the effect of small chemical doses because the restricted numbers of animals in each test (usually 200 mice and 200 rats) necessitate the application of high concentrations to obtain statistically significant results.

TECHNIQUES FOR LARGE-SCALE MONITORING

This report will explore some of the newer techniques that are highly sensitive, fast, economical, and applicable for large-scale monitoring programs for carcinogens in man's external environment. With a little effort, those techniques also can be adapted to the detection of carcinogens within the human metabolic environment. Basically, 4 groups of tests can be distinguished, each one with assets and liabilities that should be fully appreciated before its use in experimental epidemiology.

Group I includes all microbial bioassays that use forward or backward mutations as an end point (*1, 2*). The greatest advantage of these bioassays is the well-defined genetic alteration induced by the carcinogenic or mutagenic compounds and the ease with which accurate quantitative data are obtained. Their greatest disadvantage is the inability of microbial cells to activate most precarcinogens and the difficulty of some compounds to penetrate their membranes. That these problems are not insurmountable is demonstrated by the following example: A microsomal preparation of rat liver [S-9 fraction (*3, 4*)] changed most of the classical precarcinogens into their ultimate carcinogenic forms, which may then interact with the target molecule, the DNA of chromosomes (*5*). Thus bioassays are now routinely applied in combination with this activation mixture. The permeability issue is less easily overcome, although mutants of bacteria with various membrane properties can be selected (*6*).

In performing tests in group II, we try to cope directly with the activation of precarcinogens (or premutagens) into ultimate carcinogens (or mutagens). The basis for these assays is that a proper assessment of the carcinogenic and mutagenic capacity of a compound can be obtained only if the metabolic activation occurs within a living organism. Thus the idea of the "host-mediated" assay has been born (*7*). For example, various indicator organisms (yeast, bacteria, spores of fungi) are placed into a mouse that has been fed or given an injection of the test compound. After certain prescribed times, the indicator cells are

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

[2] Supported by the National Cancer Institute of Canada.

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removed and placed on culture plates, and the induced mutation frequency is estimated. Although this approach appears to be ideal, the actual results were so disappointing that host-mediated assays as performed today cannot be applied for screening a large series of compounds.

Group III tests use entire animals and end points that can be quantitated and obtained in a reasonable time after treatment. Tests to estimate chromosomal aberrations of various cell types (bone marrow cells, stimulated peripheral lymphocytes, or regenerating liver cells), the micronucleus tests (*8*), sperm anomaly test (*9*), and the dominant lethal test (*10*) have been applied to various rodents to detect the mutagenic and/or carcinogenic properties of compounds. Probably the most suitable organism is not a mammal but the common fruit fly (*Drosophila*), which can be inexpensively and copiously reared and provides an excellent tool for the detection of induced mutations (*11*). Different organs of the fruit fly seem to contain enzyme systems that can activate precarcinogens.

Bioassays of group IV have been designed to simulate the human conditions as closely as possible. For this reason, various human cells are put into tissue culture and challenged with compounds or mixtures of compounds that may be carcinogenic to man. Most (if not all) chemical and physical carcinogens and mutagens induce DNA fragmentation (*12, 13*), DNA repair synthesis (*14, 15*), chromosome aberrations, point mutations (*16*), and morphologic or neoplastic transformation (*17*). Therefore, these cell responses can be used as end points in evaluating the carcinogenic property of a compound. Considering that human cells are used as test subjects and that all end points are steps that regularly occur in carcinogenesis, the tests of group IV permit easy extrapolation to the actual human situation.

DNA REPAIR ASSAY

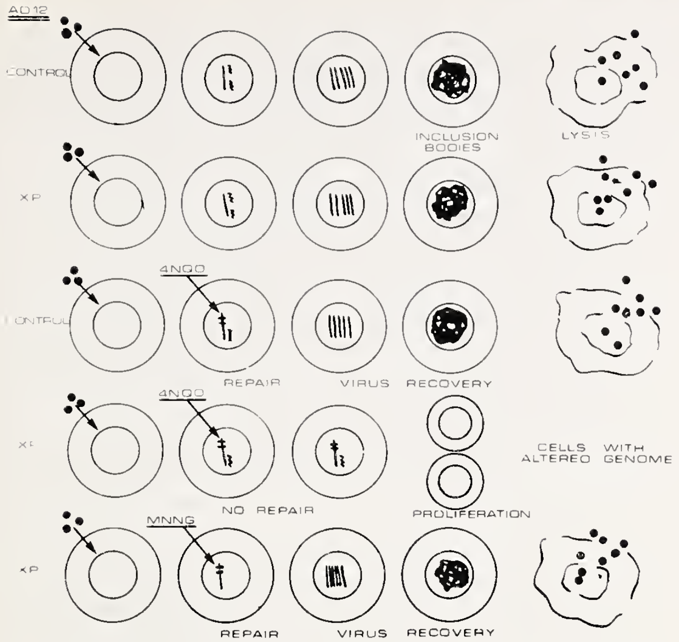
A few examples may suffice to show the adaptability of the DNA repair assay to the human situation, an advantage that should be fully exploited. The response of cells from what may be called the "healthy average" human can be compared with that of persons at high cancer risk, i.e., patients with multiple tumors, members of "cancer families" and persons accidentally or intentionally exposed to carcinogenic and/or mutagenic compounds. This approach may well yield insight into variations within the human population and permit the detection of population groups with an increased sensitivity to particular carcinogens (table 1). Table 1 shows that proper assessment must be based on several end points. For example, the type of DNA repair deficiency differs between xeroderma pigmentosum (XP) (*18*) and Fanconi's anemia (FA) cells (*19*), leading to a reduced unscheduled incorporation of [^{3}H]TdR in the former and a normal level of repair synthesis in the latter. Chromosome aberrations, on the other hand, occur spontaneously only in FA (*20*) and Bloom's syndrome (*21*). Both diseases show no abnormal level of DNA repair synthesis. Table 1 also reveals that XP cells (*22–24*) are sensitive to one set of carcinogens, and FA (*25*) or Bloom's syndrome cells are susceptible to other series of compounds. Thus the human population is composed of many groups and subgroups, each one sensitive to particular sets of chemical carcinogens or mutagens.

Cultured human cells have another great advantage over microbial organisms. They offer the opportunity of examining the interaction among chemical carcinogens, human viruses, and human genes (which can convey an increased susceptibility to chemical or viral oncogens). Chemical carcinogens can damage viral DNA, thus impairing virus replication. In this way, an infectious virus replication cycle that leads to lysis of the infected cell is changed into an abortive infection, which causes chromosome aberrations (*26*) and probably neoplastic transformation as well. Of particular interest is the influence of the XP genes on the recovery of inactivated viral DNA. The repair defect of XP cells seems to prevent the repair of damaged virus DNA, which will not resume replicating within XP cells, whereas it will do so in the cells of normal persons (*27, 28*). Genetic composition will control the result: chromosome aberrations in XP cells and lytic death in controls (*28*).

TABLE 1.—*The sensitivity of various chromosome instability syndromes toward chemical or physical carcinogens*[a]

Diseases	Spontaneous chromosome aberration	DNA repair level	Induced chromosome aberration
Fanconi's anemia	Elevated	Normal	Elevated: mitomycin
Bloom's syndrome	Elevated	Normal	Unknown
Xeroderma pigmentosum	Normal	Reduced	Elevated: e.g., aflatoxin, epoxides of cyclic aromatic hydrocarbons, UV
Down's syndrome	Normal	Normal	Elevated: X-rays

[a] The response is measured on cultured human fibroblasts by an estimation of the level of DNA repair synthesis and the frequency of metaphase plates with chromosome aberrations (breaks and exchanges).



TEXT-FIGURE 1.—Combined effect of chemical carcinogens (4-nitroquinoline-1-oxide or *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine), oncogenic viruses (human adenovirus type 12), and the cancer predisposing gene of xeroderma pigmentosum. Genetically altered cells result from only one particular combination.

The complexities of such gene–virus–chemical interactions are intimated by the variations shown in text-figure 1.

The feasibility of using DNA repair synthesis to unravel complex reactions that may occur in humans is demonstrated by the intragastric formation of nitrosated compounds (*29*) and the effect of ascorbic acid on the nitrosation reaction (*30, 31*). Several factors involved in this process account for numerous possible combinations and permutations. A solution of these issues can be achieved only by application of rapid and economic bioassays. The key tests are shown in table 2. Although no dose–response curves are given, the inhibitory effect of ascorbic acid at lower doses can be seen clearly. However, one can also note DNA damage as revealed by DNA repair synthesis and chromosome aberrations at higher doses. The chromosome aberration that results after the application of higher doses of methylguanidine (MG) + nitrite + ascorbic acid may be due to the action of ascorbic acid metabolites rather than the nitrosation products (*32*). Obviously, this dissection of complex processes into simple reactions will help reveal the proper concentration of ascorbic acid that can be added to food products to minimize its hazardous direct

TABLE 2.—*The complex interactions between MG + nitrite + ascorbic acid and Cu^{2+} and their effect on DNA and chromosomes on human cells*

Chemical compound	DNA fragmentation[a]	DNA repair[b]	Chromosome aberrations
MG	–	–	–
Nitrite	–	–	–
MG+nitrite	+	+	+
MG+nitrite+ascorbic acid			
Concentrations up to 10^{-3} M	–	–	–
Concentrations above 10^{-3} M	–	+	+
Ascorbic acid[c]	–	–	–
Ascorbic acid+Cu^{2+}	+	+	+

[a] DNA fragmentation was measured as shifts in sedimentation profiles after alkaline sucrose centrifugation.
[b] We measured DNA repair by estimating the unscheduled incorporation of [^{3}H]TdR.
[c] The ratio of ascorbic acid to nitrite was 1:1.

effects and maximize the desirable inhibitory effect on the formation of nitroso compounds.

SHORT-TERM BIOASSAYS

The usefulness of short-term bioassays for experimental epidemiology must be considered. The following areas appear to be the most likely to benefit from use of the above-mentioned test systems.

1) That the response to chemical, physical, and viral carcinogens will vary within the human population can be predicted. Knowledge about sensitive subpopulations and their clustering in space and time is essential for proper interpretation of raw epidemiologic data. Increased human sensitivity to carcinogens can be discovered by estimating levels of DNA repair synthesis (*33*), host cell-mediated reactivation of UV-irradiated intranuclear DNA viruses (*27, 28*), frequency of chromosome aberrations (chromosome instability syndromes (*34*), frequency of sister chromatid exchange (*35*), repair time between two consecutive doses (*36*), and decreased clone-forming capacity after exposure to carcinogens or mutagens. An area that will benefit particularly from the test systems is that of the estimation of "differential cytotoxicity" after challenge with a battery of chemical mutagens and/or carcinogens. The basic idea would be to select approximately 5 compounds with different chemical abilities: intercalation, base substitution, alkylation, nonalkylation, and binding. Cultured fibroblasts or stimulated peripheral lymphocytes from various high-risk groups would be exposed to this selected set of compounds and their response compared with

that of controls. Chromosome aberrations, the appearance of micronuclei, and clone-forming capacity would be adequate end points to reveal differences in sensitivity toward the action of carcinogens and mutagens.

2) A small number of genetically based syndromes (XP, FA, Bloom's syndrome) show a higher cancer risk. Chromosome instability and elevated cancer frequency are clearly linked in homozygous persons. However, their rare occurrence should not detract from the fact that the number of persons heterozygous for one or the other cancer-predisposing gene is large (according to the Hardy-Weinberg principle). If these heterozygotes should prove to have an elevated cancer risk, they may then contribute significantly to the overall incidence of tumors. The heterozygotes for the FA gene might exemplify this pattern *(37)*. Simple procedures for the detection of the heterozygous carrier of recessive cancer-predisposing genes still must be found. This task may not be easy *(38)*.

3) Measurements of carcinogens within the human metabolic system may prove to be one of the most significant contributions expected from the use of short-term tests. The presence of persons in carcinogen-contaminated environments cannot be simply equated to their exposure to those carcinogens. It is most important to estimate the actual intake of chemical compounds as well as their entry into the metabolic pathway. The analysis of urine and feces by Ames' microbial assay for carcinogens and/or mutagens *(39)* from low- and high-risk populations typifies this approach. Simple, semipurified extracts of complex mixtures such as urine and feces can be used; therefore, large-scale population studies are feasible.

4) The battery of short-term tests is being adapted for screening man's immediate environment for hitherto unknown carcinogens or combinations of carcinogens. Extensive programs were initiated by several industrialized countries and are (in part) coordinated by the United States National Institute of Environmental Health Sciences and the National Cancer Institute.

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Survey of Cancer Incidence in Alaskan Natives[1]

Anne Lanier, *M.D.*[2]

ABSTRACT—A survey of cancer incidence among Alaskan Natives for the 5-year period 1969–73 revealed fewer cases overall than expected in relation to rates in the United States. However, significantly increased risks were seen for certain sites: the nasopharynx in both sexes (with excesses over 15-fold), the liver in males, and the salivary glands, gallbladder, kidney, and thyroid in females. Compared with earlier reports, the observations suggested marked changes in cancer incidence among Alaskan Natives over the past two decades, with declines in esophageal and invasive cervical cancers, and increases in neoplasms of the lung, colon, and rectum.—Natl Cancer Inst Monogr 47: 87–88, 1977.

Alaska is a large state (586,000 square miles) with a small population (302,000 in the 1970 census). Seventeen percent of the State's population are Alaskan "Natives" (Eskimos, Indians, and Aleuts) who are believed to be originally of Asian origin. Of the Natives, 55% are Eskimo, 32% Indian, and 13% Aleut. They occupy specific areas of Alaska: the Inupiat-speaking, or northern Eskimo, along the northwest coast; the Yupik-speaking, or southern Eskimo, along the southwest coast; the Athabaskan Indians in the interior; the Tlingit, Haida, and Tsimshian Indians along the southern panhandle; and the Aleuts in the Aleutian Island chain. A large percentage live in rural areas; in 1970, 58% of the Alaskan Natives lived in villages of 500 people or less. Until recently, marked cultural and language differences existed among the groups.

Although initial reports emphasized the low incidence of cancer in Eskimos, more recent reports have described increased frequency and/or unusual histologic patterns for the following cancer sites: salivary gland, kidney, esophagus, thyroid, and nasopharynx. A report by Schaefer (*1*) suggests recent changes in patterns of cancer in Canadian Eskimos among whom the lung and cervical types have displaced salivary gland and renal cancers as the most common malignant tumors.

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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In a recent mortality study by Blot et al. (*2*), deaths from cancer in Alaskan Natives in 1960–69 were compared with expected deaths calculated from rates for Caucasians in the United States. This study indicated that, although the overall cancer death rate for Alaskan Natives did not differ from that of whites, significantly increased mortality was observed for cancers of the nasopharynx, salivary gland, kidney, esophagus, and uterine cervix.

After this report, an incidence study was done to identify all newly diagnosed cancers in Alaskan Natives during 1969–73 (*3*). The number of confirmed cases identified totaled 347 (excluding in situ carcinomas and nonmelanotic skin cancers). We compared observed cases with expected numbers and used Connecticut cancer incidence rates and 1970 census population figures (table 1). The ratio of observed to expected (O:E) cases for total confirmed cancer patients was significantly low. However, with inclusion of 26 persons for whom only a death certificate specifying cancer was available, the numbers of Native cancer cases were no longer significantly low. Significant increases in incidence were found in males for cancer of the nasopharynx and liver, and in females for cancer of the nasopharynx, salivary glands, gallbladder, kidney, and thyroid. Significant deficits in cancer incidence were observed in males for cancer of the larynx, prostate, and melanoma. Also such deficits occurred for oral cancers when nasopharynx and salivary gland sites were excluded. Among females, significant deficits were found for cancer of the breast, uterus, and lymphoma.

Observed to expected ratios did *not* differ significantly from 1 among males and females for cancer of the lung, colon, and rectum, and also in the cervix and esophagus for women. This observation would not seem to warrant comment except that, in comparison with previous reports, these ratios suggest an increased incidence in recent years of cancers of the lung, colon, and rectum and a decrease in esophageal and invasive cancer of the cervix in Alaskan Native women.

The largest O:E ratio in Alaskan Natives was observed for nasopharyngeal cancer. Nineteen

TABLE 1.—*Observed numbers of newly diagnosed cancers and O:E among Alaskan Natives by site and sex, 1969–73* [a]

Cancer site	Males		Females	
	O	O:E	O	O:E
Salivary gland	2	2.1	5	8.0[b]
Nasopharynx	9	16[b]	3	26[b]
Other oral and pharyngeal	2	0.2[b]	5	2.0
Esophagus	6	1.3	1	1.1
Stomach	10	0.9	6	1.3
Small intestine	2	2.7	0	0
Colon	21	0.9	22	1.1
Rectum	14	1.0	10	1.2
Liver	8	4.0[b]	1	1.4
Gallbladder and extrahepatic ducts	4	2.9	12	6.0[b]
Pancreas	7	1.0	5	1.2
Nose, middle ear, sinus	1	2.0	1	2.0
Larynx	0	0[b]	0	0
Lung	33	0.9	7	1.0
Prostate	16	0.6[a]		
Testes	5	1.2		
Breast			22	0.4[b]
Cervix			8	0.9
Corpus uteri			4	0.3[b]
Ovary			7	0.7
Kidney and ureter	8	1.2	8	3.1[a]
Bladder	6	0.3	2	0.5
Melanoma	0	0[a]	1	0.3
Central nervous system	3	0.5	5	1.1
Thyroid	0	0	9	2.8[a]
Other endocrine	0	0	0	0
Bone	3	2.6	1	0.9
Connective tissue	6	2.0	1	0.6
Lymphoma	6	0.6	1	0.1[a]
Leukemia	5	0.5	2	0.4
Primary unknown	12	0.8	9	1.0
	189	0.83[b]	158	0.86[a]

[a] $P<0.05$.
[b] $P<0.01$.

patients (15 males, 4 females) were newly diagnosed during 1966–74; the rates/100,000 (adjusted to Segi's world population) were 9.7 in males and 2.8 in females. An ongoing case-control study includes a questionnaire, serology for herpes group viruses, and histocompatibility antigen determination.

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History and Status of the Cancer Surveillance System of Western Washington[1]

Donovan J. Thompson, *Ph.D., and* David B. Thomas, *M.D., Dr. P.H.*[2]

ABSTRACT—A cancer registry for a population of over 2 million people was established in 1973. Although the population is predominantly white, the presence of people of Oriental stock provides a potential for migrant studies and international comparisons. Over 7,900 resident cancer cases are detected annually, and a good system for evaluating completeness of reporting and quality of collected data has been devised. To utilize the resources that the registry represents, we have a competent staff of epidemiologists and biostatisticians with academic appointments at the University of Washington and interests in cancer etiology, evaluation of care, and teaching.—Natl Cancer Inst Monogr 47: 89–91, 1977.

In April 1973, a contract between the Fred Hutchinson Cancer Research Center (FHCRC) and the National Cancer Institute (NCI) funded the development of a population-based tumor registry in six Puget Sound area counties. This cancer detection system, known as the Cancer Surveillance System (CSS) of Western Washington, became a participant in the Program for Cancer Surveillance, Epidemiology, and End Results (SEER) in November 1973. The staff has attempted to obtain information on all newly diagnosed cancer cases in the six counties since January 1, 1974.

The area covered by the CSS has a population of over 2 million people residing in urban centers (such as Seattle and Tacoma) and in rural environments. Two Standard Metropolitan Statistical Areas (SMSA) are included in the surveillance area; these are Seattle-Everett (King and Snohomish Counties) and Tacoma (Pierce County). The population estimates for the six counties for 1974 are shown in table 1. The racial composition of the total population in 1974 is estimated to have changed little since the 1970 census (table 2). As may be noted from the race and foreign-born distributions given in table 3, numbers of nonwhites and nonnative stock are small. The age and sex distribution of residents of the area for 1970 is shown in table 4.

For the purpose of environmental carcinogenesis investigations, our area has perhaps less air pollution than other areas of the West coast. We have an unusual potential for study of arsenic due to the presence of a copper smelter in Tacoma. Aircraft manufacture and shipbuilding are our major heavy industries. Forest product and lumber industries are also large employers.

Based on data for 1974, approximately 7,900 new cases of cancer, excluding nonmelanotic skin cancer, occur annually in the six-county area. An additional 2,200 nonresident cases are expected each year.

Case detection is primarily from the records of the 47 hospitals in the six-county area and is supplemented by data from selected hospitals in adjacent counties and from 5 local radiologists and 6 oncologists who do not report cases to a hospital registry. Demographic, diagnostic, and therapeutic information is obtained for each case from existing medical records. About 40% of the case records are abstracted by hospital registry personnel, and about 60% by the CSS field staff. A standard abstract form is used. Data are coded, edited, and keytaped by CSS personnel and stored in the University of Washington CDC–6400 computer.

With the incidence data, available from January 1, 1974, we will eventually be able to calculate incidence rates specific for any cancer type by such personal characteristics as age, sex, marital status, and race. An address geo-code recorded for each case will allow studies of clusters and calculation of rates by county and groups of census tracts or blocks, when indicated. Long-term continuation of the CSS will, of course, also provide temporal trends in incidence rates. Data for the year 1974 are currently available for analysis.

The FHCRC was the first SEER participant to be in an approved comprehensive cancer center. This center will serve as a major focus for cancer research activities in the Northwest. A core staff is available for development of special studies. Dr. Donovan Thompson is head of the Program in Epidemiology and Biostatistics (PEB) at the FHCRC. Dr. David B. Thomas, an epidemiologist, joined the staff of the FHCRC as director of CSS in July 1975. The former head of CSS, Dr. Noel

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

[2] University of Washington, School of Public Health and Community Medicine, Seattle, Washington 98195.

TABLE 1.—*Estimated 1974 population in the six-county area*

County	Population
Grays Harbor	60,100
King	1,146,200
Kitsap	104,300
Pierce	411,000
Snohomish	267,100
Thurston	83,900
Total	2,072,600

TABLE 2.—*Racial composition of total population of six-county area, 1974*

Race	Percentage
White (including people with Spanish surnames)	93.9
Black	3.2
Chinese	0.4
Japanese	0.9
American Indian	0.7
Other (including Eskimo)	0.9
Total	100.0

TABLE 3.—*Country of origin of the foreign stock (partial) estimated for the six counties*

Country	Foreign stock[a]	Foreign born
Australia	1,046	420
China	7,875	4,363
Japan	12,486	4,607
Korea	1,447	736
New Zealand	377	148
Pacific Islands	609	127
Philippines	9,689	5,807
Total	33,529	16,208

[a] At least one parent was foreign born.

TABLE 4.—*Age and sex distribution of all races in CSS in the six-county area, 1970*

Age, yr	Male	Female	Total
<5	88,533	84,647	173,180
5–9	102,636	97,455	200,091
10–14	106,608	102,330	208,938
15–19	100,266	93,405	193,671
20–24	96,856	93,758	190,614
25–29	79,560	76,667	156,227
30–34	62,581	60,628	123,209
35–39	57,384	56,234	113,618
40–44	59,194	60,063	119,257
45–49	62,046	63,897	125,943
50–54	56,471	56,192	112,663
55–59	47,650	48,860	96,510
60–64	37,429	39,987	77,416
65–69	27,036	32,413	59,449
70–74	19,362	27,504	46,866
75–79	13,810	21,140	34,950
80–84	8,742	14,050	22,792
≥85	5,781	9,900	15,681
Total	1,031,945	1,039,130	2,071,075

Weiss, is a recipient of an NCI Career Development Award and is doing full-time research in epidemiology. Dr. Lincoln Polissar, biostatistician for CSS, and Dr. Ross Prentice, senior biostatistician for the FHCRC, coordinate the statistical research efforts of the two groups.

DEVELOPING FIELD STUDIES

Field studies of cancer etiology are being developed or contemplated. In collaboration with investigators in Hawaii and California who are also associated with population-based tumor registries, Dr. John Lee is planning a case-control study of malignant melanomas. Dr. E. Russell Alexander currently is investigating the role of various viruses in the genesis of cancer of the cervix in women in this area and in Taiwan. Expansion of his local study with the aid of the CSS is a possibility. Dr. John Wright, an endocrinologist, is interested in using the resources of CSS to detect individuals with medullary thyroid carcinoma–pheochromocytoma syndrome so that he can conduct a family study. The past work (while he was at The Johns Hopkins University) of Dr. David Thomas includes case-control studies of the etiology of cancer of the cervix and breast, some of which is continuing. He also contemplates using the CSS for finding cases for inclusion in a case-control study of prostate cancer.

To describe quantitatively the type of initial treatment received by cancer patients, the CSS is using the standard SEER treatment and staging codes. In addition, for cancers of the breast, colon, and rectum, Dr. Weiss initiated collection of additional information from the medical records of all such cases in the six-county area on an experimental basis to provide experience for the SEER program. For breast cancer, the number of axillary nodes removed at mastectomy and the number of removed nodes positive for cancer are recorded. For patients with breast cancer treated with radiation therapy, the source of irradiation, dose, and fields treated also are recorded. For patients with cancer of the colon and rectum, the type of surgery performed is recorded in as much detail as is available from hospital records.

To assess the survival experience of cancer patients detected by the CSS, follow-up is requested annually for all cases. By relating survivorship to methods of treatment and taking into account stage of disease, we eventually will evaluate, at least partially, some modes of therapy. We will also study the "epidemiology of survival" by relating survivorship to various demographic

characteristics of the cases. In time, observation of temporal trends in survivorship will be possible.

EVALUATION OF CARE

A number of studies devoted to the evaluation of care received by cancer patients are underway at the FHCRC. In conjunction with several oncologists, Dr. Weiss planned an areawide evaluation of cancer care. Separate abstracts were developed and tested to record data for patients with lymphoma and cancer of the breast and ovary. It is planned to collect data on diagnostic procedures, extent of disease, and details of therapy so that an evaluation for adequacy of diagnostic measures and therapy can be made for the six-county area. Results are not yet available.

Dr. Ann Browder was awarded a research grant in June 1974 for a study of the social epidemiology of cancer, in which she sought to describe the range and variability of health services used by patients, and their timing, for selected cancers. The first cancer selected was colorectal cancer, chosen because it involves large numbers (it is the second most common cause of cancer death in men and women); the prognosis is improved by treatment in the early stages; and care is provided in many settings. The study (population-based) included all persons residing in King County who, during a defined time period, were newly diagnosed by tissue examination to have colorectal cancer. Although case finding was not conducted through the CSS, data from the latter source were used to evaluate completeness of case detection. The patient is often the only reasonable source of information regarding the sequence and timing of care, so interviews with patients at regular intervals throughout the first year of the patient's illness are the major source of data. The interaction of colorectal cancer patients and their medical providers is an interesting and complicated phenomenon. Nearly 200 patients entered Dr. Browder's study and have been interviewed at least once. Although few results are available, the success of Dr. Browder's efforts to sell her study to physicians and patients in our community, in addition to some interesting preliminary findings, bode well for this project's continuation. Plans are currently underway to extend the study to other cancer sites.

Several investigators at the FHCRC also are involved in clinical trials of various modes of treatment. These trials are independent of the CSS, but the statisticians from the PEB become involved in them. Dr. Norman Breslow has a contract with the American Academy of Pediatrics to operate the statistical center of the Collaborative National Wilms' Tumor Study.

Dr. Ross Prentice is collaborating with other investigators to evaluate therapeutic requirements for the treatment of leukemia and malignant melanoma and will soon also coordinate a local joint activity in which each of five hospitals has space designated as FHCRC Clinical Cancer Treatment Research Wards. This group will evaluate chemotherapeutic and radiologic treatment of various tumors.

WORK-STUDY TRAINING PROGRAM

The CSS has a work–study program to train epidemiologists, biostatisticians, computer specialists, and data processors to work in cancer research in conjunction with the School of Public Health and Community Medicine of the University of Washington. CSS data is available as source material to students who are writing theses. Drs. John Lee, Ross Prentice, and Polly Feigl collaborated on an application for cancer research training of biostatisticians and epidemiologists; the program was funded for 5 years beginning July 1, 1975. All professional personnel in the PEB of the FHCRC have academic appointments in either the Department of Epidemiology or the Department of Biostatistics at the University of Washington. Thus the number of individuals to provide professional guidance for students who work with CSS data is sufficient.

Cancer Epidemiology in the San Francisco Bay Area[1]

John E. Dunn, Jr., ***M.D., and*** **Donald F. Austin,** ***M.D., M.P.H.***[2]

ABSTRACT—The Third National Cancer Survey of 1969–71 included the five counties of the San Francisco–Oakland Standard Metropolitan Statistical Area. The complete cancer reporting for this area, begun by the Third National Cancer Survey, was continued by the California Tumor Registry as part of the San Francisco Bay Area Resource for Cancer Epidemiology. The population-based cancer-reporting system provided an excellent data base for epidemiologic studies, a number of which (planned or in progress) were described briefly. Those in progress include: cancer of the ovary, corpus uteri, and breast as related to child bearing, fertility, exogenous hormones, etc.; the relationship of diet to breast cancer occurrence among Japanese; diet and colorectal cancer among blacks; and the relationship of cervical cancer to cytology in Alameda County. Other study proposals are under consideration.—Natl Cancer Inst Monogr 47: 93–98, 1977.

The San Francisco Bay Area Resource for Cancer Epidemiology (RCE) includes Alameda and Contra Costa Counties of the East Bay, and San Mateo, San Francisco, and Marin Counties on the west side of the Bay. These five counties are included in the San Francisco–Oakland Standard Metropolitan Statistical Area (SMSA) of the Census Bureau and in the Third National Cancer Survey. The RCE became the continuation of the cancer-reporting system begun by the Third National Cancer Survey. The Biometry Branch of the National Cancer Institute, which financed the Survey, has continued this support for the geographically based cancer-reporting system of the RCE and is supporting similar programs throughout the United States. These programs have been given a common designation by the Biometry Branch: Surveillance, Epidemiology, and End Results (SEER).

The geographic area of the RCE is shown in text-figure 1. The population residing in the five-county area numbers slightly more than 3 million people, from whom we register about 12,000 new cancer cases a year, excluding basal and squamous skin cancers.

The composition of the population by ethnic groups at the time of the 1970 census is shown in table 1. People from many points around the Pacific Basin are represented in the Bay Area population. The Chinese, Filipino, and Japanese constitute the largest Asiatic populations. A large black population has come into the Bay Area in recent decades, largely from southern states, as has a Mexican-American population, which is not well defined by the Census. Some differences in the site distribution of cancer in certain ethnic groups are striking (table 2).

EPIDEMIOLOGY IN THE RESOURCE AREA

With a study population of 3 million with 12,000 cases of cancer a year, the RCE can perform epidemiologic research on many of the common cancer sites; this research includes studies comparing ethnic groups that differ in susceptibility to cancer of certain sites. The name "Resource for Cancer Epidemiology" was assumed because we believe we should not only conduct our studies but also those of other epidemiologists who have a proposal with merit and that is suited to the facilities of the RCE. However, our case reports are confidential, and we are not at liberty to make patients' names available outside the RCE. To circumvent this obstacle, RCE took the responsibility for all fieldwork concerned with epidemiologic studies of the cases in the Registry. The collected data with only the patients' identity removed are given to the principal investigator.

The RCE has a Technical Advisory Committee made up of representatives of other institutions in the area who have an interest in cancer epidemiology. Study proposals are reviewed by that committee, which decides on the merits of the proposals and their appropriateness for the RCE.

SPECIFIC STUDIES

Currently, the following epidemiologic studies are being conducted:

1) Our initial study (on cancer of the breast) was conducted under the RCE contract until June 1975, when it was awarded a grant. The Biometry Branch of the National Cancer Institute decided that the support of local option ad hoc studies was not suited to the SEER program contract

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

[2] California Tumor Registry, 2151 Berkeley Way, Berkeley, California 94704.

TEXT-FIGURE 1.—The five-county geographic area included in the San Francisco Bay Area Resource for Cancer Epidemiology.

TABLE 1.—*Population of San Francisco-Oakland SMSA by county and race, April 1, 1970*[a]

Race	Total	County				
		Alameda	Contra Costa	Marin	San Francisco	San Mateo
White	2,574,802	855,978	502,411	197,542	511,186	507,685
Black	330,1[illegible]7	161,282	41,620	5,042	96,078	26,085
American Indian	12,011	5,688	1,701	382	2,900	1,340
Chinese	88,108	20,072	3,088	873	58,696	5,379
Japanese	32,463	10,117	3,980	1,054	11,705	5,607
Filipino	44,056	10,597	2,763	326	24,694	5,676
Other	27,972	9,450	2,826	819	10,415	4,462
Total	3,109,519	1,073,184	558,389	206,038	715,674	556,234

[a] Data are taken from Public Use Samples of Basic Records from the 1970 Census: California. Washington, D.C.: Bureau of the Census.

TABLE 2.—*Average annual age-adjusted cancer incidence rates for selected sites in the San Francisco-Oakland SMSA for the years 1969–73* [a, b]

Site	White		Black		Chinese		Japanese	
	Male	Female	Male	Female	Male	Female	Male	Female
Nasopharynx	0.8	0.4	1.2	0.4[c]	21.8	7.4	1.0[c]	0.0
Esophagus	4.5	2.2	17.0	4.1	10.8	2.2[c]	2.8[c]	2.2[c]
Stomach	13.6	6.9	25.6	7.7	14.0	12.0	19.8	23.7
Colon	32.7	27.3	28.1	23.8	27.5	15.9	16.0	22.5
Rectum and anus	11.7	10.5	12.4	9.0	22.3	10.8	19.9	8.3
Liver	3.2	1.5	5.0	1.6	23.5	5.5	0.0	1.6[c]
Pancreas	11.1	7.1	17.5	10.3	10.6	5.9	6.8[c]	7.1[c]
Breast	0.8	88.7	1.5	64.5	0.4	49.1	0.0	44.1
Corpus	—	33.6	—	15.1	—	17.9	—	15.9
Ovary	—	15.1	—	10.2	—	7.3	—	6.0
Prostate	51.6	—	89.9	—	20.5	—	20.7	—
All cancer	336.1	306.4	390.4	258.4	292.8	231.6	157.5	187.2

[a] Rates are per 100,000 population.
[b] Counties included are San Francisco, San Mateo, Marin, Alameda, and Contra Costa.
[c] Value is based on 5 cases or less.

mechanism and should be supported by funds obtained from another source.

The original hypothesis was to look further into the apparent sparing effect of early pregnancy on breast cancer risk. The statement made in interpreting such data is that a woman who has her first pregnancy when she is in her thirties has two to three times the risk of breast cancer as one who becomes pregnant before age 20. The implication is that, if you had a cohort of young women for study and could randomly assign some of them to have early and others to have late pregnancies, the occurrence of breast cancer in the 2 groups would be in the range of the ratios stated above. However, age of pregnancy is also related to fertility; the study being conducted is an attempt to determine the role of infertility or difficulty in conceiving in breast cancer risk.

2) A second project, begun in late 1975, is concerned with ovarian cancer and its relationship to childbearing, fertility, exogenous hormones, etc. Data collection is continuing.

3) A third study, directed toward endometrial cancer and patterned after the first two, was funded by a grant and was initiated in 1976 and is now in progress.

4) Japanese-American women, who are undergoing a dietary transition, are also experiencing higher rates of breast cancer than their contemporaries in Japan. A case-control study is being conducted to examine the role of diet in the etiology of breast cancer.

5) Other work at the University of California School of Public Health at Berkeley, in which data collection is now completed, is concerned with family aggregations of Hodgkin's disease.

The following items refer to proposed projects, approved locally and awaiting review and funding from other sources:

1) A study of childhood cancer including diagnosis, treatment, and outcome; the role of family members; primary and referral physicians; and the availability of medical insurance has been proposed. The principal investigator is at the University of California School of Public Health at Berkeley.

2) Dr. J. A. H. Lee (University of Washington), a leading epidemiologist in studies of melanoma, has requested that the Bay Area SEER Group be co-principal investigators of a case-control study of the epidemiology of malignant melanoma involving several areas of the United States. The nature of the research would be to evaluate the effect of certain phenotypic and behavioral factors that may have importance in the etiology of these tumors.

3) Melanoma mortality and relationship to occupation (in California) also are being studied. Certain published and unpublished data sources (*1*) have suggested that specific occupations have an elevated risk of death from malignant melanoma; however, the data were based on small numbers of deaths. The plan is to perform a case-control, death certificate study on approximately 2,000 melanoma deaths and 3,000 matched controls. The completed grant proposal is pending internal review and processing and has not been approved as yet (November 1975).

4) Cytology specific for cervical cancer screening has been available for over 30 years. With increasing use of the procedure, a large proportion of the population of women have had this

TABLE 3.—*Age-adjusted incidence rates[a] for colon and colorectal cancer[b] from the Third National Cancer Survey[c] for the north, south, and west regions of the United States by race and sex, 1969*

Area[d]	White				Black			
	Males		Females		Males		Females	
	Colon	Colon and rectum	Colon	Colon and rectum	Colon	Colon and rectum	Colon	Colon and rectum
North	34.5	52.7	30.8	42.4	34.5	53.3	30.5	43.2
South	28.5	41.3	26.0	34.7	23.5	30.8	22.7	30.3
West	37.3	55.4	30.8	42.3	21.2	34.7	20.5	27.8

[a] Rates are computed per 100,000 and adjusted to 1970 United States population.

[b] Colon excludes rectosigmoid; rectum includes rectosigmoid.

[c] Data are taken from Preliminary Unpublished Report, Third National Cancer Survey, 1969 Incidence, Biometry Branch, National Cancer Institute.

[d] North: Detroit, Iowa, Minneapolis-St. Paul, Pittsburgh. South: Atlanta, Birmingham, Dallas-Ft. Worth. West: Denver, San Francisco–Oakland.

examination. The question now being raised is: Where is the evidence that this examination has substantially reduced the occurrence of clinical invasive cervical cancer and deaths from this cause?

In Alameda County, we have incidence rates for carcinoma in situ and invasive cervical cancer and for deaths from cancer of the cervix from 1960 to November 1975. We also have survey results of knowledge and use of cervical cytology examinations from population studies in 1962 and 1973. In this same area, 80 to 90 invasive cervical cancer cases and 30 to 40 deaths from cancer of the cervix still occur each year. A grant proposal has been submitted on research to determine the cytology experience of these patients and why they have come to diagnosis with clinical disease. This study is funded and is in progress.

EPIDEMIOLOGIC STUDY OF COLORECTAL CANCER IN BLACKS

Funded by a grant from the National Cancer Institute and in cooperation with the RCE, the Kaiser Foundation Research Institute is conducting, concurrently, a comparative study of blacks in the Bay Area and in Atlanta, Georgia. The project worker, who is black, doing the field study was recruited by the RCE and conducts, under our supervision, the interviewing of persons who develop colorectal cancers and who are living in the five Bay Area Counties, as identified by the incidence-reporting system. The completed interviews (without patient identification) are delivered to the principal investigator.

The rationale for the study is the low rates of colon cancer found in the white and black populations of the South compared with other sections of the United States. Data from the Third National Cancer Survey are shown in table 3 (Biometry Branch, National Cancer Institute: Unpublished report). Colorectal cancer rates for the white population in the West are comparable with those in the North, and both are greater than for Southern whites. Northern blacks have gained parity with Northern whites, but the Western black population has rates comparable with Southern blacks. About three-fourths of the Bay Area blacks have migrated from the South, and it is expected that their colorectal cancer rates will be moving upward toward the rates for the white population. The Bay Area study is directed toward determining whether the dietary changes presumed to be taking place in the black population are reflected in the ongoing incidence rates for colorectal cancer.

The study started in September 1973, and data collection continued for 3 years. About 80 colorectal cancers occur annually among blacks in the five Bay Area Counties. Almost all the interviews took place at home because the few cases distributed through the many hospitals make in-hospital collection impractical. The incidence-reporting system is the means of case identification. The study protocol requires three controls for each case: two are matched to the case by age, sex, race, and hospital. The third is matched on the personal variables but drawn from the Kaiser multiphasic-screened population.

Our information is based on the progress report prepared by Drs. Dales, Friedman, and Ury on data gathered during the first year of the project. The data include 120 subjects: 42 cases, 50 hospital controls, and 28 persons from the multiphasic screens. At the time of the data analysis for the progress report, the full complement of control subjects had not been interviewed. This lag, of course, is inevitable since the identification of controls must follow that of cases.

The study is centered primarily on dietary information. The reference point for obtaining this information was 3 years prior to time of interview. Study subjects also were asked whether any dietary changes took place at the reference point time as compared with preceding time. If they did, eating habits at this earlier time were queried. The additional variables for which data were collected dealt with residence history, socioeconomic factors, disease categories responsible for hospitalization of controls, body build, use of tobacco and alcohol, bowel habits, disease experience, and, for women, their pregnancy history, etc.

Obviously, the data analyzed in this report (collected in the early period of the study) are based on a small number of subjects and are unbalanced between cases and controls for the reasons stated earlier. With the reservations these conditions impose, the results of this early analysis will be reviewed.

The socioeconomic variables placed the cases at a slightly higher level than the hospital but a little below the multiphasic controls. Males were heavier than their controls; the opposite was true for women. Alcohol and tobacco were used excessively. For men the excess tobacco use was most marked in relation to cigar smoking. Constipation was a frequent complaint, although the investigators point out that patient bias has to be considered in this finding. The occurrence of other diseases did not distinguish cases from controls except that cases reported intestinal polyps more often than did the controls.

Because dietary data were the main concern, the interview was geared to the collection of information on the frequency with which 89 food items were used. Eight graded frequency options ranged from "never" or "almost never" to "at least once a day." In the analysis, the frequency options were assigned a numerical score corresponding roughly to the number of times a month the food was eaten. A median consumption frequency score for all subjects combined was determined for each food item. Comparisons were made between percentages of patients and controls equaling or exceeding the median score.

In addition to comparisons on individual food items, cases and controls were compared as to consumption of groups of food items combined on the basis of common nutritional components. For every subject, the consumption frequency scores for the individual items comprising each food group were totaled. The sum scores for the food group were then analyzed in the same way as those for the items.

One food group designated as "Southern" was hypothesized as representing an index of retention of traditional Southern eating habits. No difference between cases and controls was noted in a comparison in the frequency of use of these traditional Southern foods. A comparison made between cases and controls as to frequency of beef consumption (including processed) indicated a reduced risk of colorectal cancer associated with the highest level of consumption. This is contrary to the findings of a case-control study of Japanese-Americans in Hawaii (*2*) and Seventh-Day Adventists in California (*3*). Similarly, food groups high in saturated fats were inversely related to colorectal cancer occurrence. However, this group of foods is heterogeneous, and the amount consumed perhaps would be a better measure than frequency.

The Hawaiian case-control study of Japanese found an association between large bowel cancer occurrence and consumption of string beans. This was not sustained in the present data or found in the Seventh-Day Adventist study.

Grains, vegetables, and fruits were selected for high and low residuals of indigestible roughage. Again, no relationship to colorectal cancer cases was found.

These findings are preliminary and may be changed as the data from the completed study become available. The investigators made the point that finding a relationship between beef consumption and colorectal cancer may depend on a threshold phenomenon. The low beef consumption in the traditional Japanese diet and the vegetarian and semivegetarian diets of most Seventh-Day Adventists may be necessary for the effect of increase of beef consumption on colorectal cancer occurrence to become evident. Also, with larger numbers of cases, it will be possible to look at anatomic sites in the large bowel separately. The sigmoid colon may be more sensitive in reflecting dietary associations.

One interesting finding in this early analysis was the fact that 44.4% of women with colorectal cancer had never borne children as compared with 12.1% of the female controls.

Thus far, the findings from this study do not indicate that colorectal cancer among blacks increases with a change from Southern food to that more characteristic of Northern or Western urban whites. An association between beef as a specific food item and colorectal cancer among Hawaiian Japanese and Seventh-Day Adventists in Califor-

nia and between legumes as a specific food item and colorectal cancer in Hawaiian Japanese was not supported. However, these statements are tentative because of the small amount of data available for analysis in this report.

OCCUPATIONAL CANCER COHORT STUDIES

In the mid-1950's, the California State Health Department conducted a prospective study of a number of occupational groups to determine the risk of lung cancer associated with specific occupations. The groups under suspicion of high lung cancer risk had been identified in an earlier case-control study of patients and controls. Complete occupational histories were obtained; analysis of the data indicated a number of occupations were represented more frequently among the lung cancer cases than among the controls. Occupations selected for prospective study included welders, asbestos workers, cooks, marine engineers and firemen, painters, and electric bridge crane operators; public utility workers served as a control population. The size of the population considered as minimal for prospective follow-up was 5,000; union organizations cooperated in making their memberships available.

Over 68,000 men were included in the combined occupational groups. Lung cancer occurrence was determined by a check of the listing of study subjects against the annual mortality listing for California. The 5- to 7-year follow-up of these populations was done manually until the last 2 years when computer matching was begun.

This cumbersome and time-consuming prospective study had the limitation of identifying deaths only, but this was not a particular disadvantage for lung cancer risk determination, considering the rapid progress of this disease from onset to death in most cases. However, it is an inefficient methodology for cancers of other sites for which survival of a sizable proportion of cases occurs.

The cancer-incidence system of the five Bay Area counties now provides a means of monitoring a cohort of the population that can be identified and for which the variables necessary for computer matching can be obtained. We are again approaching the craft unions of these five counties to assemble populations of occupational groups to monitor for cancer occurrence in an ongoing manner with the cancer-reporting system. Initially, membership lists and necessary data for computer matching will be acquired from local union offices. Monitored populations then will be available for more specific studies of individual members, who would be contacted for their work history and specific occupational exposures.

In addition to union membership, occupations requiring licensing provide another means of identifying a population cohort. The carcinogenic potentialities of hair dyes are of current interest. Beauticians and cosmetologists are not highly organized in the Bay Area, but all must be licensed. Information has been made available to us for the more than 20,000 licensees in the Bay Area. We also have collected data concerning the asbestos workers' union membership and the firefighters.

Other crafts of interest include: butchers and meat wrappers, laundry and drycleaning workers, painters, roofers, bakers, bartenders, and metal polishers. Some locals of the plumbers union have requested inclusion in the study. Additional occupational groups can be added depending on study interest and availability of an appropriate Bay Area population.

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Cancer Surveillance Program in Los Angeles County [1]

Thomas M. Mack, ***M.D., M.P.H.*** [2]

ABSTRACT—A system of rapid surveillance for cancer in the population of Los Angeles County was studied, and the methodology was compared with traditional population-based registries. Comparisons with the Third National Cancer Survey were also made, and the pattern of malignant melanoma occurrence in Los Angeles residents was described.—Natl Cancer Inst Monogr 47: 99–101, 1977.

Southern California might have been designed with epidemiology in mind. The population is immense and resides in cities and towns, on farms, mountains, beaches, and deserts. Most of the people are not natives. Four racial groups are represented in large numbers; within each of these, sizable specific ethnic subgroups can be identified. Industry, both past and present, has diverse carcinogenetic implications. Area residents range from wealthy to extremely poor. Large populations of both old and young people can be found in geographic as well as cultural contiguity. Anyone who has followed the history of Los Angeles knows that religious and behavioral diversity almost transcends belief.

The potential epidemiologic resources of this area are second to none. To examine these resources for purposes of cancer epidemiology, we chose to maintain a cancer surveillance system on the 7 million residents of Los Angeles County and on the 20,000 residents of a nearby retirement community.

Our program originated in 1971 as an epidemiologic adjunct to a program in oncovirology (*1*). It has subsequently developed into a complete epidemiologic program and now is incorporated administratively into the Epidemiology and Biostatistics Unit of the Los Angeles County–University of Southern California Comprehensive Cancer Center. Since the program is the agent of Los Angeles County for cancer surveillance, hospitals and physicians are legally free, under provisions of the California Health and Safety Code, to report each new diagnosis of cancer.

All but 1 of the 183 hospitals in the County willingly participate in the surveillance system at present. Staff members (usually pathologists) have been designated to serve as liaison professionals in each institution. The hospitals in each of the adjacent counties have been visited, and their medical records were examined for evidence of cancer diagnoses in residents of Los Angeles County and of the retirement community. Each hospital in which many diagnoses are made has been added to the roster of hospitals periodically visited.

The goals of our program are essentially identical to those listed by Dr. C. S. Muir. Although the principal emphasis is on the formulation and testing of etiologic hypotheses, our data are also used for 1) cancer program planning, 2) evaluation of cancer care and other programs, and 3) studies of the detection, diagnosis, and therapy of cancer. We serve individual hospitals and investigators by providing rosters and data of local or particular interest. An annual report to each participating hospital summarizes the year's experience at that hospital and in the County by site, age, sex, and geographic area of residence.

Our methods do differ from those of most population-based cancer registries. Our surveillance of pathology reports is active rather than passive. Only when no alternatives are available do we rely on persons with other administrative responsibilities and loyalties. Each of our technicians has a monthly circuit of hospitals, some of which are large and require several visits per week, and others that need to be visited only every few months. All pathology files (surgical pathology, peripheral blood hematology, bone marrow, autopsy, and cytology) are screened at each visit, and both demographic and medical information are abstracted from hospital face sheets and charts. Pathology reports and other highly pertinent items are photocopied and appended to the abstract form. The algorithm for coverage of each hospital is different and depends on its administrative and recordkeeping idiosyncrasies. Because of these differences, discharge indices and tumor registries are only routinely screened in some hospitals.

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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TABLE 1.—*Ratio of age-adjusted incidence[a] of cancer in Los Angeles County, 1972–74 compared with that in the entire United States, 1969–71[b]*

Selected site	Males				Females			
	Whites[c]		Blacks		Whites[c]		Blacks	
	N_{LA}[d]	RR_{LA}[e]	N_{LA}	RR_{LA}	N_{LA}	RR_{LA}	N_{LA}	RR_{LA}
Breast	71	1.43	9	1.56	8,891	1.23	713	1.27
Colon, rectum	3,620	1.00	267	1.05	4,120	1.00	338	1.08
Lung, bronchus	4,970	0.95	651	1.04	2,125	1.52	174	1.28
Prostate	3,792	0.98	515	1.08	—	—	—	—
Uterus (corpus)	—	—	—	—	3,443	1.70	151	1.40
Bladder	2,110	1.27	89	1.31	809	1.26	64	1.83
Stomach	858	0.84	124	0.92	607	0.85	78	1.03
Uterus (cervix)	—	—	—	—	958	0.70	227	0.65
Ovaries	—	—	—	—	1,438	1.06	96	1.00
Pancreas	709	0.80	74	0.61	534	0.72	83	1.02
Leukemia	749	0.81	72	0.93	556	0.76	61	1.07
Melanoma	629	1.74	6	0.76	575	1.45	6	0.81
Esophagus	240	0.70	96	0.80	142	1.08	53	1.54
Total, all sites	24,270	0.98	2,567	1.01	30,388	1.16	2,781	1.14

[a] Data are standardized to the 1970 Census population.
[b] Data are taken from (2).
[c] Patients with Spanish surnames are excluded; other racial groups also are not reported here.
[d] N_{LA} means number in Los Angeles on which rate is based.
[e] RR_{LA} means risk ratio for Los Angeles=Los Angeles rate/United States rate.

At the same time, all death certificates originating in the County, or returned there because of County residency, are screened for mention of cancer. Questions concerning individuals with neoplasms who are not already accounted for in the system are referred to the technician responsible for the hospital in question. When no hospital is identified, inquiries are made to the attending physician, the nursing home, or the coroner.

Thus a second difference between our program and other population-based registries is that we routinely limit our criteria for registration to two factors: pathologic evidence of cancer and evidence of cancer at time of death. Therefore, in our system, we routinely miss those patients who have clinical but not pathologic evidence indicating cancer and who either survive or die in circumstances in which that evidence is unavailable at the time the death certificate is being completed. We believe these patients are few and of limited epidemiologic utility. At present, we are conducting a sample survey of hospital sources of clinical diagnoses to measure the magnitude of the losses. Incidence rates derived from our program are comparable generally with those from the Third National Cancer Survey (table 1), although there is some variation by site and race.

The third aspect of the program that does not correspond to usual registry practice is the selection of information to be abstracted. Our system emphasizes prediagnosis characteristics and the basis for the pathologic diagnosis. It deemphasizes clinical staging, the details of treatment, and the hospital course. This system is used because of the epidemiologic importance of the prediagnosis characteristics and the costs in time and money of gathering treatment details.

In addition to anatomic site and subsite, histologic type, and date of first pathologic diagnosis, we obtain "rough" (tentative) information about the length and principal feature of the presenting illness. Our data include age, sex, marital status, race and ethnicity, religion, birthplace, and residence (coded by census tract) of the patient. For all men under age 65 (and for most other patients), we obtain the occupation by industry at the time of diagnosis. We find that Los Angeles hospital patients' charts provide this information with fair regularity.

Although a general extent of disease classification is obtained at the time of first treatment, we do not expend the time and training necessary to abstract uniformly detailed extent of disease and treatment. Approximately 60% of the cancer diagnoses in Los Angeles County residents occur in hospitals with tumor registries, and when necessary, our routine information can be augmented with additional clinical detail for specific categories or samples of patients. Since we need not wait for the clinical work-up to be completed, surveillance of large hospitals is complete within 1 or 2 weeks of diagnosis.

For similar reasons, we do not routinely conduct follow-up on accessed patients other than by

monitoring County death certificates. We have the future option of monitoring statewide death certificate tapes and of conducting standard follow-up on specific sites or samples of patients.

The privacy of individual records is maintained at least as well as in the hospitals. Written records are kept in secure systems. Computerized medical information can be used for identification only with the use of codes and in the physical presence of our personnel.

To illustrate the value of our descriptive information for purposes of hypotheses formulation, I will describe the pattern of malignant melanoma in Los Angeles County residents (this material will be reported in detail elsewhere).

Our data confirm those from other sources by the incidence rates that are inversely associated with pigmentation by race. Rates for whites in Los Angeles are high and confirm the known inverse association with latitude. With minor irregularities, an inverse association with the latitudinal origin of European-American patients' surnames when compared with the surnames of other cancer patients also can be found.

The pattern of melanoma incidence in whites varies with specific anatomic site. Data of incidence of melanoma occurring on the trunk are relatively high in men, as are rates of melanoma occurring on the legs of women. Rates of melanoma on women's legs and men's trunks show stronger direct associations with age and social class (as measured by mean income and education of census tract residents) than do rates of melanomas on men's legs and women's trunks. Within Los Angeles County, except for that predicted by income and race, variation by geographic area is slight. Surprisingly, rates at some sites in both sexes are higher in native Californians than in those born in other regions of the United States or abroad.

Rates by occupation and industry for whites indicate that persons with outdoor occupations have low rates, whereas those working indoors (including those with less prestigious occupations) have higher rates. Rates of melanoma on the extremities tend to occur with a consistent slight preponderance on the left side, especially on women's legs.

Although the specific etiologic reasons for this pattern of occurrence are unclear, certain questions are definitely posed for further exploration in the case-control study now being designed. Emphasis must be placed on measures of skin pigmentation, on questions concerning habits of recreational exposure to the sun, on life-long sun exposure, and on sun protection preferences and experiences. Through careful questioning of melanoma patients and appropriate controls, we hope that knowledge of the etiology of malignant melanoma will be increased immensely.

We find that our system functions well for etiologic research and program planning and that it also provides an adequate base for other purposes. It is not only rapid but extremely flexible, since technicians can be diverted temporarily from surveillance to other ad hoc activities. Personnel can be chosen on the basis of capability and motivation rather than experience, central quality control can be imposed easily, and audits in the field can be made periodically. Currently, this capability is achieved for less than $20 for each newly diagnosed case.

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Cancer Incidence in the Mexican American [1]

Herman R. Menck [2]

ABSTRACT—Mexican Americans of Los Angeles County, both those born in Mexico and in the United States, were at lower risk to all sites of cancer combined, than other whites. These Mexican Americans were at increased risk to some specific cancers, including those of the stomach, gallbladder, and cervix. For those tumors for which racial differences existed, clear migrant patterns were present.—Natl Cancer Inst Monogr 47: 103–106, 1977.

Mexican Americans occupy a genetically and environmentally distinct position in the population of the United States. This factor may be related to differences in their health patterns (*1*). They are the descendants of those Spaniards and other Europeans who intermarried with American Indians from 1500 A.D. to date (*2, 3*). Early Indian cultures were based on the cultivation of corn (*2*); since that time, much of the protein intake of Mexican Americans has been derived from their consumption of corn and beans, with relatively small amounts of animal protein and fat (*4, 5*). Economically, Mexican Americans are a disadvantaged minority and are employed in jobs of low status (*6*). Mexican American women bear children early and frequently have large families. Demographically, the population is young.

The number of Mexican Americans, present in large numbers in Los Angeles County (table 1), increased 62% during the sixties. The County's annual rate of growth differed markedly by ethnic group, with the minority populations increasing rapidly. The increase of 1 million people in Los Angeles County between 1960 and 1970 occurred within the black and Spanish surname subpopulations. The total population of Los Angeles County did not increase between 1970 and 1975 (Martin HD: Personal communication). Growth rates by ethnic group since the census are not available.

Several Spanish indicators have been used to classify Mexican Americans of Los Angeles County, including Spanish mother tongue, acknowledged Spanish heritage, and Spanish surname (table 2). The most inclusive Spanish indicator in Los Angeles County was mother tongue; however, the total of those reporting Spanish heritage was nearly as large as the number reporting Spanish mother tongue. Fewer residents had Spanish surnames, and these included those of Spanish heritage other than Mexican and some of non-Spanish heritage. Our cancer data were collected from hospital records, and the only Spanish indicator available for our use was the Spanish surname, which we used as representative of the Mexican-American population of Los Angeles County. We simplified the classification of nativity by dichotomizing into Mexican-born and others.

Many differences in cancer incidence rates for Mexican Americans and other whites were interesting. Among males and females, a deficit of cancer of the oral cavity, oropharynx, larynx, and lung was found (table 3). As these sites are strongly associated with smoking (*10–16*), we can postulate that Mexican Americans smoke less or metabolize tobacco-related carcinogens more slowly (*17*). Clear nativity patterns were present with the greatest deficit seen in the immigrants; rates of Mexican Americans born in the United States approach those of the other whites.

In contrast to these anatomic sites, though small in number, the incidence rates for nasopharyngeal and nasal cancers in Mexican Americans were high. The cancer incidence rate for these sites also has been reported high in American Indians (*18*). Environmental carcinogens other than cigarettes have been implicated in the etiology of these cancers (*19–21*), and the anatomic relationship between the sites and their functions is consistent with Schoental's (*22*) suggestion that inhaled carcinogenic mixtures, e.g., wood smoke, are physiologically separated, with the actual site of cancer determined by the physical properties of the various airborne components.

Although many Mexican Americans have stomach cancer, neoplasms of the colon are infrequent in this ethnic group. These findings are consistent with similar observations by Haenszel and Correa (*23*). Variations among countries and religious sects, compatible with a dietary etiology, have been described for both cancers.

In females with Spanish surnames who live in Los Angeles, rates of biliary tract cancer were

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TABLE 1.—*Population by ethnic group, Los Angeles County*[a]

Race	1960[b]	1970[c]	Annual rate of growth, %
Other white	4,880,694	5,070,915	0.4
Black	460,947	762,844	5.2
Spanish surname	576,716	935,584	5.0
Japanese	77,314	104,994	3.1
Chinese	19,286	41,500	8.0
Other	27,474	115,978	15.5
Total	6,042,431	7,032,075	1.5

[a] Total population in 1975=7,020,700 (Martin HD: Personal communication).
[b] Data are taken from (*7*).
[c] Data are taken from (*8, 9*).

TABLE 2.—*Frequency of Spanish indicators in the population, Los Angeles County, 1970*[a]

Spanish indicator	Percent of total population
Spanish surname/mother tongue	18.1
Spanish mother tongue	17.0
Spanish heritage	16.6
Mexican	13.0
Other	3.6
Spanish surname	13.3
Mexican	9.9
Puerto Rican	0.2
Cuban	0.4
Central/South American	0.6
Other Spanish	0.6
Non-Spanish	1.6

[a] Data are taken from (*9*).

markedly higher than those of either Spanish-surnamed males or non-Spanish females. The distribution in Los Angeles County is given in table 3 by subsite. Of these biliary tract cancers, 28% occurred in the bile ducts, including the Ampulla of Vater. The predilection of biliary tract cancer for the aged is well known; only rarely do these cancers occur before age 45. Cancers develop in the bile ducts at a younger age than in the gallbladder. In Los Angeles County, 1 of every 3 patients with cancer of the bile duct was under age 55, whereas 1 of 11 persons with cancer of the gallbladder was in the same age category.

Lieber (*24*) reported a correlation among cholelithiasis, carcinoma of the gallbladder, and diabetes. Other investigators have observed an association between cholelithiasis and cancer of the gallbladder (*25, 26*), with a greater prevalence of the former in obese females (*27, 28*). Diet (*29*) and female hormones (*30*) have been implicated in gallbladder disease. Female Pima Indians (*31*) experience high rates of diabetes, cholelithiasis, and cancer of the gallbladder. This common finding suggests that these conditions are etiologically related. The rates for cancer of the liver are also higher in the male and female Mexican Americans than in other whites.

Age at first intercourse, parity, and socioeconomic status are known predictors of breast and cervical cancer (*32, 33*); our observations are consistent with Mexican-American reproductive

TABLE 3.—*Standard incidence ratios (100 for other whites) for Mexican Americans, by sex and nativity, for selected sites, Los Angeles County, 1972–74*

Site	Male				Female			
	Immigrant		Indigenous		Immigrant		Indigenous	
	No.	SIR[a]	No.	SIR[a]	No.	SIR[a]	No.	SIR[a]
Buccal cavity	14	42[b]	36	63[b]	11	68	28	62
Nasopharynx	0	0	6	160	2	202	1	53
Other pharynx	5	71	8	64	2	68	3	40
Stomach	50	214[b]	53	159[b]	23	148	39	192[b]
Colon	30	43[b]	88	91	27	35[b]	77	73[b]
Gallbladder	5	216	10	303	37	621	26	363
Extrahepatic bile ducts	6	154	5	63	11	316	8	156
Nose, sinuses	4	273	2	78	2	160	2	92
Larynx	11	58	18	58	3	65	3	40
Lung	61	41[b]	142	63[b]	33	59[b]	54	57[b]
Breast	—	—	—	—	96	40[b]	372	83[b]
Cervix uteri	—	—	—	—	102	292[b]	125	159[b]
Other male genital organs	2	122	10	312[b]	—	—	—	—
Bladder	18	29[b]	41	47[b]	10	47	16	56
Cancer, all sites	449	62[b]	892	78[b]	559	69[b]	1,252	86[b]

[a] SIR=standard incidence ratios.
[b] $P<0.05$.

patterns and socioeconomic status. Similar patterns of culture and cancer risk were demonstrated in American Indians (*18*). The high risk of cervical cancer may be explained partly by patterns of medical care, since hysterectomies are performed less frequently among Mexican Americans. In addition, cytologic screening in the city has probably been less available, even in recent years. Cervical carcinoma in situ is not included in the frequencies cited. In Mexican Americans born in Mexico, the rate of invasive cervical cancer actually exceeds that of breast cancer. Incidence rates of other types of cancer involving the male genitals are higher in the Mexican Americans.

The sum of cancer in all sites was lower in Mexican Americans of both sexes. Bladder and lung cancer were markedly lower in Mexican Americans than in other whites. The site-by-site distribution in the Spanish-surnamed was strikingly similar to that reported for the American Indian; the highest cancer ratios common to these groups were those for cancer of the stomach, liver, gallbladder, nasal passages, cervix, and male genital organs, and the lowest ratios were for lung and bladder cancer. Mexican Americans residing in large numbers in the United States, like other distinct racial and ethnic groups, show a unique pattern of cancer incidence. Although genetic factors may be partially responsible for some of these differences, it seems clear from migration and site patterns that most determinants are environmental. Further studies of individual cancers in the ethnic milieu of Los Angeles seem warranted.

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Rationale and Methods for an Epidemiologic Study of Cancer Among Seventh-Day Adventists [1]

Roland L. Phillips *and* **Jan W. Kuzma**[2]

ABSTRACT—Considerable evidence was found that Adventists are a low-risk population to develop cancer of many sites. Adventists have numerous unique life-style and dietary habits with great variability within the population in adherence to these practices as well as considerable variation in duration of exposure to these characteristics. Thus this study population will likely be extremely productive in identifying dietary habits or other life-style characteristics that are etiologically related to various cancer sites.–Natl Cancer Inst Monogr 47: 107–112, 1977.

Seventh-Day Adventists are a small, conservative, evangelical religious denomination with about 500,000 members in North America and 3 million worldwide, many of whom follow a unique life-style. By church proscription, they completely abstain from smoking and the use of alcoholic beverages. The church highly recommends, but does not require, that its members follow other unique dietary practices. For example, many follow a lacto-ovo-vegetarian diet, which is free of any type of meat, poultry, or fish, but does contain milk products and eggs. Virtually all Adventists abstain from pork products and other biblically defined unclean meats. In addition, they avoid the use of coffee, tea, and cola beverages, hot condiments and spices, and highly refined foods. As a natural consequence of these restrictions, they make abundant use of fruits, whole grains, vegetables, and nuts in their diets. These dietary habits have been recommended by the church for over 100 years.

In general, Adventists emphasize quality education and family life and are deeply committed to their religion. Although no specific data are available, we suspect that they have rather conservative social mores. The church encourages marriage within the Adventist group and discourages divorce. Although exercise and rest are highly recommended, no data exist to indicate that Adventists rest and exercise more regularly than most individuals. Many people hypothesize that Adventists have decreased stress and anxiety as a result of their deep religious commitment, but no one has really attempted to measure this characteristic.

PREVIOUS MORTALITY STUDY IN ADVENTISTS

In 1958, investigators (*1–5*) carefully identified approximately 47,000 Adventists living in California, who they studied for 8 years. Causes of death were tabulated as recorded on death certificates. Text-figure 1 shows the results of this study of cancer deaths in terms of standardized mortality ratios (SMR). Age- and sex-specific cancer mortality rates from the general California population were used to calculate expected deaths in resident Adventists. Thus an SMR of 100 would indicate that Adventists have the same mortality rate for that site as the general California population. The vertical lines indicate 95% confidence limits. As expected, Adventists have extremely low mortality rates for cancer sites that are related to cigarette smoking or alcohol consumption. However, they also show significantly lower mortality ratios for other major classes of cancers unrelated to cigarettes or alcohol, such as gastrointestinal cancers, those of the reproductive system, and leukemia. For neoplasms of the kidney and central nervous system and lymphomas, Adventists do not differ significantly from the general population. Among the cancer sites unrelated to smoking or drinking, with the exception of leukemia, the reduced risk in Adventists is limited to sites that have the most evidence of being related to dietary customs.

Text-figure 2 details the Adventist SMR for specific gastrointestinal cancers. For both sexes, the risk of death from cancer of the colon, stomach, and pancreas is about 60–70% that of the general population. For gallbladder cancer, Adventists do not differ significantly from the general population. The risks of postmenopausal deaths from cancers of the breast, ovary, and uterus (endometrium and unspecified) are significantly below those of the general population, whereas mortality from prostate cancer is not significantly different from that of the general population (text-fig. 3). The low rates for cancer

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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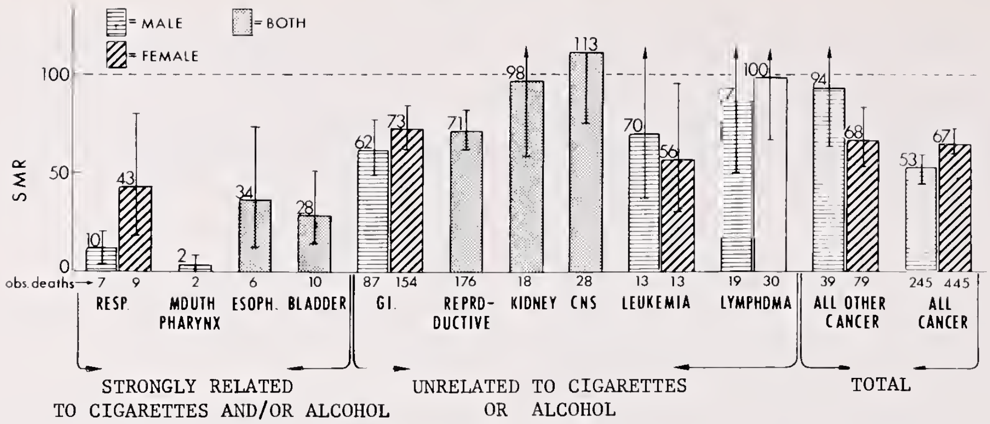


TEXT-FIGURE 1.—SMR for various cancers among California Adventists by sex, age 35+, 1958–65. In this and subsequent figures, SMR=(O/E)×100 where O=number of observed deaths in Adventists during 1958–65, and E=number of expected deaths derived by cumulating the yearly expected deaths (obtained by applying the yearly age- and sex-specific California death rates to the corresponding age and sex group in the Adventist population at risk at the beginning of each year. Confidence limits of 95% are indicated. CNS includes benign and unspecified CNS neoplasms.

of the cervix in younger Adventist women are most likely related to their conservative sexual practices.

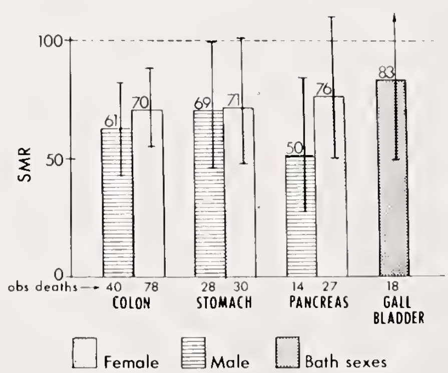
At present, little is known about the hormone status of Adventist women, but it probably is associated with their low risk of breast, ovary, and endometrial cancer. We have recently begun a study of the relationship of diet to hormone status in young Adventist girls.

REASONS FOR LOW CANCER MORTALITY IN SEVENTH-DAY ADVENTISTS

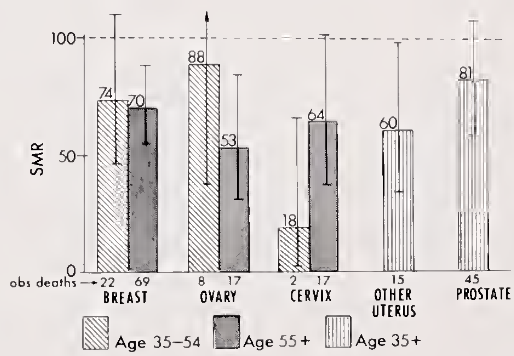
Since Adventists have a low risk of death from most cancers, their low mortality rates may be simply a reflection of better cancer survival rates. To evaluate this possibility, we presently are beginning a study to compare survival rates for major cancer sites in Adventists with those of other patients admitted to the same hospitals. Obviously, the fact that Adventists abstain from smoking and drinking accounts for their low risk of cancer of the lung, mouth, esophagus, and probably the bladder. However, for the sites unrelated to smoking and drinking, their unique dietary habits or other life-style characteristics may account for the low cancer mortality rates. An equally tenable hypothesis is that selective factors that determine who becomes and remains an Adventist may wholly or partially account for their cancer mortality rates being lower than those of the general population. Adventists are by no means a representative sample of the general population; indeed, they are a very select group.

Life-style Versus Selection

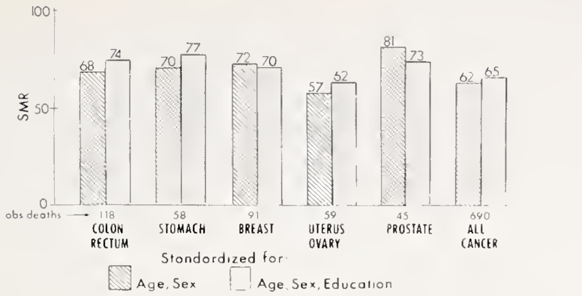
If we can rule out better survival rates as a major factor, we are left with two basic hypotheses to account for the low cancer risk: life-style or selection. The first suggests that one or more of



TEXT-FIGURE 2.—SMR for gastrointestinal cancers among California Adventists by sex, age 35+, 1958–65.



TEXT-FIGURE 3.—SMR for cancers of the reproductive system among California Adventists by age, 1958–65.



TEXT-FIGURE 4.—SMR for various cancers among California Adventists, age 35+, when education was included as a parameter in SMR calculation, 1958–65. We adjusted data for education by partitioning the annual age-, sex-, cause-specific California mortality rates for the period 1958–65 according to the 1960 education-specific mortality ratios for United States whites (6).

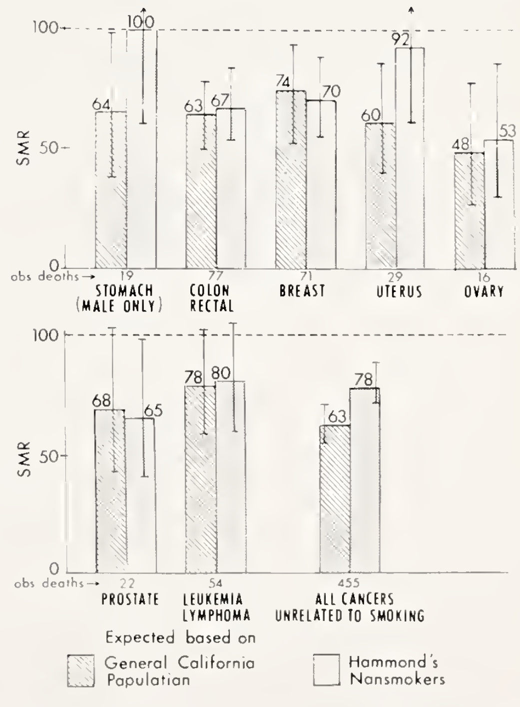
the components of the typical Adventist diet or life-style result in a lower cancer risk. However, before the low mortality risk for cancer sites unrelated to smoking and alcohol can be attributed to some other aspect of the life-style, one needs to resolve the crucial issue: Can this reduction in risk be explained by selective factors? Undoubtedly, numerous factors determine which persons in the general population choose to become and remain Seventh-Day Adventists, and it is conceivable that such factors might be unrelated to dietary habits or other life-style characteristics and yet significantly influence cancer mortality rates.

Socioeconomic status and educational level are examples of selective factors. The proportion of Adventists who have some college education is about twice that of the general population. Using data from Kitagawa and Hauser (6) on education-specific death rates for a random sample of deaths in the United States, we adjusted the Adventist mortality ratios for educational status. Text-figure 4 shows that such adjustment did not significantly change mortality ratios for any of the major cancer sites.

As another approach in evaluation of the selection hypothesis, we recalculated the SMR by using a more appropriate general population group to calculate expected deaths of Adventists. It seemed more appropriate to compare our data with those published in Hammond's (7) prospective study of non-Adventists (both groups answered questionnaires). Furthermore, since almost all Adventists are nonsmokers, we used the data on nonsmokers in Hammond's population to calculate expected deaths. The *solid bars* in text-figure 5 depict SMR's for Adventists recalculated with Hammond's nonsmokers as the standard or comparison population. Stomach and uterine cancers are the only sites for which the gradient between Adventists and the general population was significantly reduced by this approach. The persistence of the differentials between Adventists and the general population for cancers of the colon, breast, ovary, and prostate, as well as leukemia and lymphoma, weakens the hypothesis that nonsmoking or selective factors account for the differential for these sites.

Dietary Habits

Therefore, it seems reasonable to concentrate on determining which of the unique characteristics of the typical Adventist life-style might account for their apparent low risk of cancer. The evidence mentioned above suggests that better educational status is not a major factor in the differential. Aside from cervical cancer, the evidence is not convincing that religiosity or conservative social mores could account for the low Adventist risk of major cancer sites. Similarly, little or no evidence exists that regular exercise, rest, or decreased stress influence the differential. Thus diet remains the prime explanatory factor for the reduced risk of cancer sites unrelated to smoking or drinking. Data from recent studies



TEXT-FIGURE 5.—SMR based on different standard populations for various cancers among California Adventists, age 45–79, 1958–65.

(*8*) are consistent with the hypothesis that dietary characteristics of the Adventists might be related to lower risk of cancer at various sites. For example, Adventists have a low intake of all proteins; both animal studies and the international distribution of cancer morbidity (*9*) indicate that total protein or calorie intake may be related to various forms of cancer. Primarily based on intercountry correlations, Armstrong and Doll (*9*), Wynder et al. (*10*), and Howell (*11*) provided suggestive evidence that animal protein and/or fat intake may be causal factors for cancers of the colon, breast, ovary, endometrium, prostate, kidney, or pancreas. Haenszel et al. (*12*) have specifically identified beef as a possible etiologic agent for colon cancer, and Burkitt (*13*) firmly believes that lack of fiber intake may increase colon cancer risk. Hill (*14*) has suggested that anaerobic gut bacteria produce carcinogens from bile acids and other steroids. Since output of these substrates is increased by diets high in fat and animal protein, Adventists would tend to have a low output as demonstrated by Wynder and Reddy (*15*) on a small sample of Adventist vegetarians.

We have some preliminary evidence that Adventist women may have a later menarche (*16*) and a lower frequency of obesity (*17*), which are low risk characteristics for neoplasms of the reproductive system, as observed by MacMahon et al. (*18*) and deWaard and Baanders-van Halewijn (*19*). Schmauz and Cole (*20*) and others have suggested that coffee intake may also be related to cancers of the urinary tract, and Breslow and Enstrom (*21*) have recently hypothesized that alcohol intake, more specifically beer intake, may affect a person's susceptibility to rectal cancer. Perhaps as a result of their vegetarian diet, Adventists have a lower intake of benzo(*a*)pyrene and nitrosamines (*22, 23*) and a higher one of flavones, which are strong inducers of the enzyme systems responsible for detoxifying such carcinogens (*24*). In addition, they may have a higher intake of vitamins A and C, recently suggested as possible protective agents against certain chemical carcinogens (*25*). Thus it seems reasonable to suggest that the typical Adventist diet may protect against many of the major sites of cancer.

Preliminary data on dietary habits are available in a recent survey of about 250 Adventists and a smaller sample of their non-Adventist neighbors in the southern California area. About 25% of Adventists are lifetime vegetarians; an equal number stopped eating meat, poultry, or fish, and have become vegetarians; and about half currently eat meat, poultry, and fish. Our survey showed that those who currently use meat are less heavy consumers than their counterparts in the general population. Among the Adventists, 60% consume meat fewer than three times/week, whereas almost 60% of the non-Adventists eat it at least once daily or more often. In our survey, 46% of the Adventists who formerly ate meat changed to a vegetarian diet late in life. The group who stopped eating meat when they were under 20 years of age may be of particular interest because they consumed meat only in the early years of life.

In the same survey, Adventists were asked to report any changes in their intake of other foods that may be related to cancer: sugar and sweets, coffee, white bread, whole milk, eggs, and fried foods. For each of the foods listed, respondents were asked to indicate whether at any time in their life they had permanently decreased their usual consumption. The choices ranged from "no decrease" to "stopped entirely." From 40 to 60% of the participants reported either stopping or considerably decreasing their intake of these foods. The mean age of change was about 40 years of age, which is about 7 years later than that at which former meat eaters became vegetarians. This suggests that the first dietary habit that converts adopt is the vegetarian diet, and then they progressively adopt other church recommendations on diet, such as low intake of sweets, refined foods, milk, eggs, and high-fat foods.

ADVANTAGES OF ADVENTIST STUDY POPULATION

Because of these unique dietary habits, Adventists comprise a useful group in which to study the relationship of diet to cancer risk. The voluminous work on diet and coronary heart disease indicates that a large variation in dietary habits within a single population is necessary to demonstrate a relationship between food intake and risk of a chronic disease (*26*). Adventists, who are homogeneous in many respects, vary considerably in their dietary habits. Also many Adventists have changed from the typical American diet to one typical of their religion. These characteristics suggest that we can test hypotheses in the Adventist group that might be difficult or impossible to test in other populations. For example, the hypotheses that fat, fiber, or beef intakes are related to colon cancer might be tested among Adventists but be difficult to test in other populations in the United States because of uniformity in intake of these nutrients. The large variation in use of these

products by Adventists may also allow us to determine whether a dose–response relationship exists. Because of the shift in dietary habits in many young Adventists, we may be able to determine whether exposure to these nutrients early in life have a greater influence on cancer risk than do recent ones.

A recent case-control study among Adventists (41 with colon cancer and 106 controls) was designed to test the hypotheses that intakes of high fat or low fiber, or both are associated with risk of colon cancer. The highest relative risk was obtained for those who ate meat 20 years ago. However, current consumption of several other foods showed relative risks of 2:3. All the foods that showed statistically significant relative risks are consistent with the hypothesis that fat and/or meat consumption relates to risk of colon cancer.

METHODOLOGY OF CURRENT ADVENTIST STUDY

Because of the unique advantages this population offers, a prospective study of the more than 100,000 Adventists living in California was initiated in 1974. The objectives of the Adventist Health Study are:

1) To confirm, with incidence data, the previously observed low SMR for cancers unrelated to smoking, and

2) To identify specifically those components of the SDA life-style that account for the apparent low risk of cancers unrelated to smoking.

Through questionnaires mailed to households containing Adventist members, we are developing a study population (approximately 41,000) from whom we will obtain detailed information about their life-styles. The participants will be under surveillance for 5 years so researchers can identify newly diagnosed cancer cases and deaths.

Questions on life-style will measure dietary habits in three ways: the frequency of *current* use of specific foods, *past* intake of specific foods, and a quantitative estimate of *current* intake of major nutrients. We shall look particularly at those dietary items related to cancer risk, as suggested by data obtained from recent human and animal studies: total calories, saturated versus unsaturated fat and total fat, animal versus vegetable protein and total protein, complex carbohydrates such as starch, natural sucrose (contained in unrefined products such as fresh fruits), added sucrose, other sugars, fiber, caffeine, cholesterol, and possibly various vitamins and minerals.

We intend to make comparisons on incidence and mortality rates for cancer of various sites in relation to adherence to various components of the Adventist life-style: vegetarian or nonvegetarian; light, medium, or heavy consumers of specific foods or nutrients. We will also compare persons who have been Adventists for many years with recent converts. We also have planned a substudy to ascertain in as great detail as possible how Adventists differ from the general population in their health status, accessibility to medical care, dietary habits, and frequency of known risk factors for cancer.

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Papanicolaou Testing and Hysterectomy Prevalence in Low-Income Communities: A Survey in Los Angeles County[1]

Elizabeth Stern, Marilyn Misczynski, Karla Damus, *and* Anne Coulson[2]

ABSTRACT—A survey of the prevalence of Papanicolaou (Pap) testing and of hysterectomy and a feasibility study were conducted in low-income communities with high rates of cervical cancer, identified by an analysis of mortality and case rates. Although about 90% of the women reported having had a Pap test some time in the past, a much smaller percentage reported regular testing. For example, in the 5 years preceding the study (1971–75), about a quarter of the women had been tested only once and about a third not at all. No evidence of a secular change in hysterectomy prevalence in these communities was found.—Natl Cancer Inst Monogr 47: 113–119, 1977.

An apparent correlation exists between decreasing mortality from cancer of the cervix and increasing cytologic screening (*1*, *2*). However, a trial of the impact of cytologic screening on mortality has not been performed, and the evidence is inconclusive that the secular drop in mortality is a consequence of screening (*3*, *4*). The rationale for mass screening for cancer of the cervix is based on the assumption that there is a curable preinvasive stage of the disease, which is readily detectable by the Papanicolaou (Pap) test (*5*, *6*); the validity of this natural history model has not been established (*7–12*).

The effectiveness of a screening program can be evaluated most successfully in areas where sizable unscreened groups of high-risk women reside, with screening allocated to one geographic location and withheld from another. Objections to such withholding, on ethical grounds, can be countered with the argument that the test is not yet generally available in routine medical care. Difficulties in the assessment of rates are to be anticipated, particularly in the control group.

An advantage of locating a screening study in the United States is the availability of reliable population denominators and cancer incidence registries. Communities with high rates of cervical cancer, similar in age distribution, ethnic background, and socioeconomic status, and comparable in availability of health services, thus can be identified. For example, a mass screening program would be introduced into the experimental community, while the control community would have access to whatever screening is normally available. The disadvantage of conducting a clinical trial is the high level of background screening reported by recent surveys, which indicate widespread use of the Pap smear, except possibly for women in older age groups or who are in the lower socioeconomic groups and ethnic minorities (*13–15*).

Los Angeles County was considered as a possible location for an experimental trial because the County includes geographically defined areas with sizable numbers of low-income, ethnic-minority women, presumably at high risk for cervical cancer, providing the necessary large population base. In studying methods to test the effectiveness of mass cytologic screening, we made an analysis of cervical cancer incidence and mortality and obtained information on the prevalence of Pap testing and of hysterectomy procedures by a survey of women living in high-rate areas. The feasibility of recruiting women into community screening clinics was assessed in two of the neighborhoods surveyed.

MATERIALS AND METHODS

Case and death rates by health district.—The distribution of the female population of Los Angeles County by age and ethnic background was derived from the 1970 Census of Population and Housing (*16*). At the time of our study, Los Angeles County was divided into 26 health districts that are geographic aggregates of census tracts; the number of women by age and ethnic group was available for each health district.

Data on cervical cancer deaths were obtained from California death certificate tapes, which include the census tracts of residence. The total numbers of deaths for 1969, 1970, and 1971 were averaged to yield a mean annual death rate. Data on new cases of invasive cervical cancer for 1972 and 1973 were obtained from the Cancer Surveillance Program of the University of Southern California.

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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Case and death rates for each health district were computed and age-adjusted to the overall County rate. Age-specific death and case rates by ethnic group were computed for each health district (*17*). Black women of the South, Southeast, Southwest, and Compton Health Districts (inner city) and the Spanish-surnamed and other white women in the El Monte Health District formed part of the identified high-risk group.

Sampling scheme for the household survey.—For the household survey, the four inner city health districts were combined; the fifth district, El Monte, was sampled separately. The survey sampling scheme for the inner city was a stratified sample based on income. Tracts in each stratum were weighted by their population of women aged 35–54. For each income stratum, the tracts were listed, and the number of women aged 35–54 years in each tract was added cumulatively. To ensure an adequate number of women from the lowest income stratum, we selected 4 of the 50 tracts with median incomes under $6,000, 1 from the 39 tracts in the $6,000–6,999 range, and 1 from the 26 tracts in the $7,000–7,999 range. Since no significant differences were found when variables were examined by income group, we did not use an income-weighting factor in calculating the results for the inner city. Tracts with median income over $8,000 were not included. We selected a tract by drawing a random number, and the first tract in the list with a cumulative population that included the random number was used. An example of the selection procedure in census tracts with less than $6,000 per year median income is shown in table 1. If the random number drawn were 742, tract 2225 would be selected, as that value lies within the cumulative range 695–1109.

The 38 tracts in the El Monte health district were reviewed. Of these, the 16 comprising the city of El Monte were most suitable for the household survey in terms of age-eligible women, income distribution (1970 median income below $10,000), and inclusion of Spanish-surnamed persons. These tracts were sampled without stratification for income but with weighting for number of women aged 35–54, as in the inner city. Five tracts were selected at random.

TABLE 1.—*Selection procedure for survey*

Tract No.	Female population, 35–54 yr	Cumulative population
2,215.02	331	331
2,222	363	694
2,225	415	1,109
2,218	287	1,396
↓	↓	↓

Women aged 35 and over were to be interviewed. Thus the survey sample was drawn from a population of approximately 100,000 women aged 35 and older in 131 low-income census tracts. We estimated that contact with approximately 1,500 households would yield interviews with 400 age-eligible women.

Blocks in each selected tract were identified from census maps. Four blocks were then randomly selected in each tract. The fourth block selected was used only if the minimum number of households was not available in the first three blocks. Each selected block was outlined, with its surrounding streets and/or other boundaries. We identified the starting corner by using random numbers. Interviewers were instructed to start with the *n*th household, *n* being a randomly drawn number between 1 and 10. Every sixth household after that initially selected was contacted.

The survey was done during November and December of 1974. No advance publicity through media, mail, or other community channels preceded the survey. Women were contacted directly at their homes. Trained interviewers questioned all female household members 35 years and older as to hysterectomy and previous Pap testing. Information was recorded on the number of households vacant, inaccessible, or with no eligible women. When no one was at home, one or two recalls were made. Women not interviewed included those who refused to grant an interview, and those who were never at home.

Study on recruitment.—Two neighborhoods were selected from the surveyed census tracts on the basis of proximity to the center where the tests were to be performed. Recruitment began on one preselected block, and adjacent blocks were added sequentially. In the selected Compton and El Monte neighborhoods, 1,250 contiguous households were contacted to achieve recruitment into the clinics of approximately 200 women aged 25–55 years. The age range of 25–55 years would be considered optimal in a controlled trial of the effectiveness of a screening program on morbidity and mortality from cancer of the cervix, since the lower bound includes the ages at a sharp increase for invasive cancer of the cervix, whereas the upper bound excludes ages at high death rates from all causes.

In each of the two geographic areas, four clinic sessions were offered over a 2-week period in April 1975. A female nurse practitioner performed the clinical procedures, which included

TABLE 2.—*Female population of Los Angeles County by age and ethnic derivation*[a]

Ethnic group	Age, yr									Total
	Under 5	5–14	15–24	25–34	35–44	45–54	55–64	65–74	Over 74	
White, non-Spanish	153,033	369,283	389,797	294,908	275,494	337,727	268,072	193,022	147,376	2,428,712
Spanish-surnamed	80,200	154,049	125,393	99,469	80,454	54,647	33,389	19,885	9,661	657,147
Black	41,811	91,936	71,166	58,945	47,752	38,622	26,804	15,689	7,664	400,389
Oriental[b]	5,228	12,717	13,134	11,821	12,870	9,184	3,733	3,220	1,891	73,798
Other	7,579	13,098	13,703	15,015	9,096	5,287	3,538	1,903	991	70,210
Total	287,851	641,083	613,193	480,158	425,666	445,467	335,536	233,719	167,583	3,630,256

[a] Source is 1970 U.S. Census of Population and Housing.
[b] Group includes Japanese and Chinese.

TABLE 3.—*Invasive cervical cancer incidence and mortality in Los Angeles County and selected health districts*

Area	Female population, 1970	Mortality rates[a]			Incidence rates[b]		
		Crude	Age-adjusted[c]	SMR[d]	Crude	Age-adjusted	SIR[e]
Los Angeles County	3,490,892	6.0 (5.6–6.5)[f]	—	—	15.0 (14.1–16.0)	—	—
Selected health districts:							
Inner city							
Compton	120,670	6.4 (4.0–9.5)	8.4 (5.3–12.5)	1.40	19.9 (14.7–26.5)	24.7 (18.2–32.9)	1.64
Southwest	155,488	8.1 (5.8–11.2)	8.7 (6.2–12.0)	1.44	22.2 (17.4–28.2)	24.3 (19.0–30.9)	1.62
South	72,575	8.3 (4.9–13.1)	12.0 (7.1–18.9)	1.98	19.3 (12.8–28.0)	24.7 (16.4–35.8)	1.64
Southeast	53,631	14.3 (9.1–21.5)	14.3 (9.1–21.5)	2.37	26.1 (17.4–37.8)	27.4 (18.3–39.7)	1.83
El Monte	141,811	6.6 (4.4–9.5)	9.8 (6.5–14.1)	1.63	18.0 (13.4–23.7)	22.6 (16.8–29.8)	1.50

[a] Values are based on average annual death rate 1969–71; deaths/100,000 population.
[b] Data are based on average annual case rate 1972–73; new cases/100,000 population.
[c] Values are adjusted to the age distribution of females in Los Angeles County.
[d] SMR=standard mortality ratio.
[e] SIR=standard incidence ratio.
[f] Value represents 95% confidence interval.

breast and pelvic examination and the Pap test; the services were free.

After the conclusion of the pilot clinics, we attempted to contact nonparticipants among the El Monte women to ascertain if they differed from clinic participants. The nonparticipants were those who broke appointments, refused to make appointments, or were never at home.

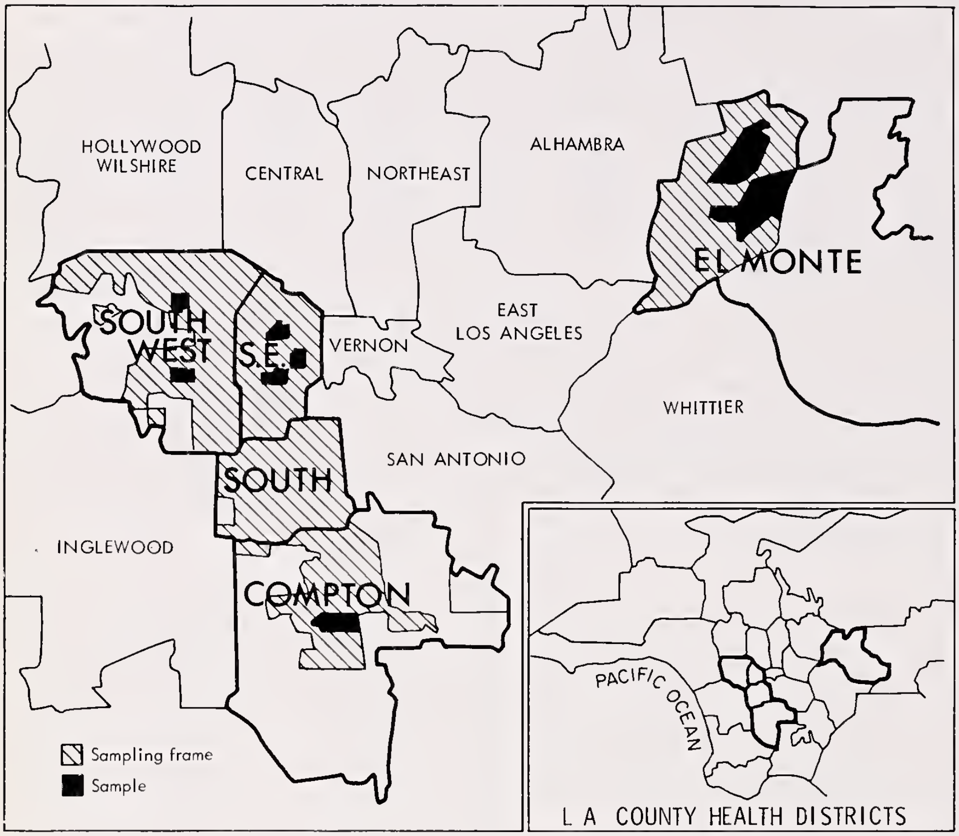
RESULTS AND DISCUSSION

The breakdown by age and ethnic derivation of the 3,630,256 female residents of Los Angeles County is given in table 2. About two-thirds of the females were white non-Spanish; the numbers of black and Spanish-surnamed women were substantial. Large groups of women assumed to be at high risk for cervical cancer were thus available for study.

Incidence and mortality rates for invasive cervical cancer are shown in table 3. Crude and age-adjusted rates are given for health districts selected as possible communities for a trial of the effectiveness of Pap screening. The adjusted mortality rates are higher than the overall County rate; and the lower bound of the confidence limit for the adjusted rate is higher than the upper bound of the County rate in three health districts for mortality, and in all five for incidence of invasive cervical cancer. The highest rates are noted in Southeast, the district with the lowest income in the survey.

The geographic locations of the health districts with high rates of cervical cancer are shown in text-figure 1. The area of the sampling frame in the inner city and in El Monte is indicated on the map, as well as the sampled census tracts used in the survey.

The survey found someone at home in 76% of the 1,429 households. On initial or recall visits, 17% were not at home. Seven percent of the



TEXT-FIGURE 1.—Household survey sampling scheme.

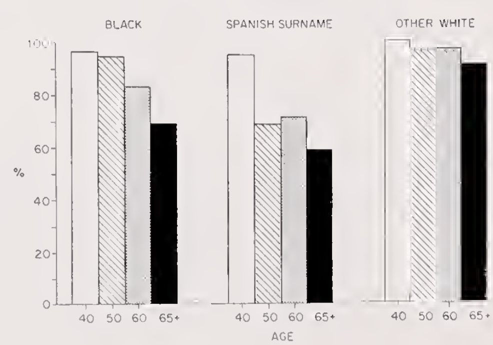
households were vacant. Of the 526 women who were over 34 years of age, 72% were interviewed and 28% refused. A difference in nonresponse between the inner city and El Monte was not apparent. In the inner city, 98% of the 200 women interviewed were black; in El Monte, of the 179 women interviewed, 33% were Spanish surnamed, 64% were other white, and the remaining 3% were black. The results were based on the interviews of the 379 age-eligible women.

Women with Spanish surnames were younger than blacks and other whites; only 30% were 55 or older, compared with 39% of blacks and 48% of other whites. They appeared to have less stability of residence, judging from the finding that 49% of other whites and 43% of blacks had lived in their homes more than 5 years, compared with 32% of Spanish-surnamed women.

The ethnic groups did not differ in their knowledge of the Pap test; 97% of the women surveyed had heard of it. The rate of positive replies to the question: "Have you ever had a Pap test?" was 76% for Spanish-surnamed, 93% for other whites, and 88% for blacks. Only 12% of the total had never been tested. The breakdown by age is given in text-figure 2. Among other whites, the proportion having a Pap examination was high in all age groups.

Sixty-two percent of the blacks, 44% of the women with Spanish surnames, and 44% of other whites answered that their last Pap test was performed within the past 2 years (table 4) in response to the question: "How long ago was your last Pap test?"

To determine whether screening was systematic (i.e., do women have regular Paps and at what



TEXT-FIGURE 2.—Percentage of women reporting previous Pap tests by age and ethnic group.

TABLE 4.—*Interval since last Pap test (Household Survey)*

Time lapse, yr	Black		Spanish-surnamed		Other white		Total[a]	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Tested								
<2 years	123	62	26	44	59	51	209	55
2–5 years	37	19	15	25	19	16	72	19
>5 years	15	8	4	7	30	26	50	13
Never tested	24	12	14	24	5	4	45	12
Unknown	0	0	0	0	3	3	3	1
Total	199	100	59	100	116	100	379	100

[a] Total includes 5 women from other ethnic groups.

intervals?), we asked the women attending the pilot clinics this series of questions:

Did you have a Pap test in 1975?
" " " " " " " 1974?
" " " " " " " 1973?
" " " " " " " 1972?
" " " " " " " 1971
Did you have a Pap test before 1971?

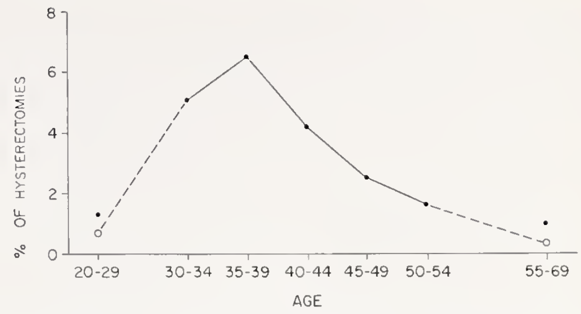
In answer to our question about testing prior to 1971, we found that 44% of the women had been tested by that time. The responses shown in table 5 indicate that within the past 5 years, about 38% of the women were tested at least twice and 61% only once or not at all. Duplication of the test has been suggested as a means of reducing the false negative rate (*9*). Although the prevalence of Pap testing was high, it was evident that many women were not tested regularly.

We attempted to verify statements on prior Pap tests by checking the laboratory records of patients receiving care within the County health system. Sixty percent of the household survey responses and 78% of the pilot study responses were verified from the laboratory file. Unverified responses may have been due to name change, incorrect spelling, or misfiling; also, some of the reported Pap tests may have been taken at facilities other than those named or were never taken.

TABLE 5.—*Frequency of Pap tests (Pilot Clinics)*

Tested	Black		Spanish-surnamed		Total[a]	
	No.	Percent	No.	Percent	No.	Percent
Within past 5 years						
2 or more tests	24	46	34	31	66	38
1 test only	17	33	30	28	49	28
0 tests	9	17	11	10	21	12
Never	2	4	32	29	36	21
Unknown	0	0	2	2	2	1
Total	52	100	109	100	174	100

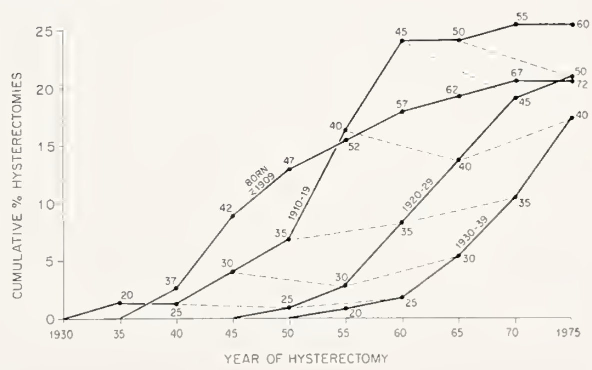
[a] Values include 13 women from other ethnic groups.



TEXT-FIGURE 3.—Age-specific percent of hysterectomies in population-at-risk. *Open circles* based on average of cases in an age group encompassing 5 yr.

Information on prevalence of hysterectomy in the community is important in a study of screening effectiveness. Nineteen percent of the black, 15% of Spanish-surnamed, and 24% of other white women reported having had a hysterectomy. Estimated age-specific incidence of hysterectomies (text-fig. 3) was based on response to the question, "When did you have your hysterectomy?" Highest rates were between ages 30 and 44 years, with the peak at 35–39 years.

The cumulative percentage of hysterectomies by age for four birth cohorts is given in text-figure 4. The oldest, born before 1910, shows the lowest cumulative proportion of hysterectomies. The remaining cohorts have essentially similar proportions of hysterectomies for each age group. An apparent leveling off occurred after 45 years of age in the three cohorts; the youngest cohort had not yet reached that age. For women born from 1910 to 1939, no increase in age-specific hysterectomy rates over the past 30 years was indicated.



TEXT-FIGURE 4.—Age-specific prevalence of hysterectomies in four birth cohorts based on the 1975 survey of women aged 35+ of low income. *Numbers* on cohort lines are the midrange ages of the cohort at the calendar year indicated. *Dashes* connect the cohorts at equal ages (e.g., at age 35, the hysterectomy prevalence for the cohort born 1910–19 was 7%; for the cohort born 1920–29, 8%; and for the cohort born 1930–39, 10%.

When the feasibility study was done during the spring of 1975, as a pilot endeavor, actual participation of women in a screening program was assessed and clinic and laboratory procedures were tested. Of the 50% of eligible women who made an appointment, almost three-quarters completed the clinical procedure. Participating women were mainly black and Spanish surnamed; responses to the Pap test and hysterectomy questions were comparable to those of black and Spanish-surnamed women in the household survey.

Pelvic examinations in the course of the clinical work-up provided a means of verifying the answers to the questions on hysterectomy. The statement and examination findings as to whether the uterus had been removed corresponded perfectly. The women were not well informed about whether a total or subtotal hysterectomy had been performed. In 95% of the cases examined, the cervix had been removed.

About 50% of the age-eligible women contacted would not participate, a majority giving as a reason that they had a private physician. After the pilot clinics were concluded, we attempted to obtain comparable background information from the nonparticipants and found that most of the women who refused to participate had been given Pap tests recently by their doctors. The level of previous testing was higher in this group of refusers than in the group of women who made appointments but did not keep them.

CONCLUSIONS

The survey provided interview information on the prevalence of Pap screening and hysterectomy in low-income women aged 35 and older from the inner city, which has a predominance of black women, and from El Monte district, where both Spanish-surnamed and other white women reside. The results are important because the information on background screening is limited in areas with high rates of cervical cancer in older women and in women who are not likely to seek or are not eligible for available health programs.

Other surveys (*13–15*) based on more representative samples of women nationwide indicate a high prevalence of Pap testing overall, but with lower prevalence among low-income, older, and ethnic minority groups. Our survey, focused on disadvantaged groups in Los Angeles County in locations where cervical cancer rates are high, showed an apparent higher prevalence of Pap testing when compared with data from the National Center for Health Statistics and the Gallup Poll (*14–15*).

This comparison on prevalence of the Pap test does not provide information on the frequency of testing. Further questioning in our pilot clinics indicated little evidence of regular testing: in the 5 years preceding the study, only 38% reported two or more tests; 28% had been tested only once and 33% not at all.

A single screening may be a serious limitation in overcoming the technical and diagnostic errors of the test, which may partly explain the high rate of cervical cancer in the surveyed communities. Also, because of the prolonged latency of the disease, the impact of screening on invasive cervical cancer may not have had a chance to become apparent, although we found that almost half the women had been tested more than 5 years ago. No evidence of a secular change in hysterectomy prevalence that would significantly affect the cervical cancer rates was found.

Some women, especially those who are highly mobile, may not receive notification of their abnormal test results, or, if aware of abnormal findings, they may be hesitant to seek appropriate treatment. These factors may contribute to the high rate of cervical cancer. On the other hand, women who do not participate in screening programs may constitute a reservoir of cancer cases. In our survey of nonparticipants, we found that these women were in fact being tested. It is also possible that detection and successful treatment of preinvasive cancer may not result in significant reduction of clinical cancer of the cervix, as invasive cancer may not always develop via the preinvasive route.

Answers to these questions could be provided by a controlled study, in which the outcome based on the introduction of a high-quality systematic screening program into one community is compared with the outcome in a control community having access to testing available from existing medical services.

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Immunosurveillance and Cancer: Epidemiologic Observations[1]

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ABSTRACT—To evaluate the immunologic surveillance theory of cancer, we reviewed the epidemiologic observations that have been made on cancer risk among population groups with immune deficiency. Lymphoproliferative neoplasms predominate in various groups, most notably renal transplant recipients treated with immunosuppressive agents and patients with primary immunodeficiency syndromes. In some immune disorders, specific forms of nonlymphoid neoplasia seem to occur excessively, although the patterns are not clear-cut or consistent. The available epidemiologic evidence fails to support the concept that immunosurveillance mechanisms are generally involved in carcinogenesis but does provide clues to immunologic processes that may predispose to particular neoplasms.—Natl Cancer Inst Monogr 47: 121–126, 1977.

In recent years, clinical and epidemiologic observations have indicated that persons with immunologic deficiency are prone to cancer (*1*). This information has been used to support the "immunologic surveillance" theory proposed by Thomas (*2*) and Burnet (*3*). They hypothesized that in all individuals, clones of neoplastic cells with new surface antigens arise repeatedly but are then rejected and eliminated by the cellular immune system of the host. Whenever this system is impaired, cells may accumulate unchecked to form a malignant tumor. This concept is attractive and widely accepted, but challenges have been raised recently, particularly by experimentalists (*4–6*), so that a review of the epidemiologic evidence seems in order.

THERAPEUTIC IMMUNOSUPPRESSION

The best documented information linking immune defects to carcinogenesis comes from studies of persons receiving kidney transplants and large doses of immunosuppressive agents to prevent rejection. Until recently, clinical series of post-transplant cancers were sufficient to indicate the elevated risk of lymphoma, but the evidence on other neoplasms was not clear-cut. In 1973, we reported a follow-up study of 6,297 patients from the Kidney Transplant Registry of the American College of Surgeons (*7*). Compared with population-based figures from the Connecticut Cancer Registry and the Third National Cancer Survey, transplant recipients experienced a sizable elevated risk of lymphomas and some increase of skin and selected other cancers.

We have recently updated the analysis of registry data, now encompassing nearly 9,000 transplant recipients. Eight patients were excluded because of evidence that immunosuppression permitted tumors to be "transplanted" with the donor kidney (4 lung cancers, and 1 each of melanoma, renal cell carcinoma, hepatocellular carcinoma, and laryngeal cancer). For the remaining de novo tumors, lymphomas developed at a rate 25 times greater than expectation (table 1). The increase was confined to non-Hodgkin's lymphoma, with a 45-fold excess, consisting mainly of reticulum cell sarcoma (histiocytic lymphoma). Many of the tumors originated in the brain, usually a rare site for presentation of lymphoma.

The risk of other cancers was elevated twofold but no across-the-board effect was observed, as might be anticipated by the immunosurveillance hypothesis. Certain common tumors, such as breast and large bowel, did not occur excessively. Instead, the increased risk was limited to particular cancer sites; i.e., liver and biliary tract (primarily hepatocellular carcinoma), lung (primarily adenocarcinoma), bladder, leukemia, melanoma, and soft tissue sarcoma. Since the cut-off date for this analysis, further reports of these tumors to the Registry suggest that the excesses are real.

Although immunologic mechanisms seem responsible for the predisposition to post-transplant lymphoma, their contribution to other neoplasms is unclear. The apparent excess of lung adenocarcinoma in transplant recipients is of special interest, since a raised incidence of "spontaneous" lung adenomas was reported in mice that received neonatal thymectomy or antilymphocyte serum. Prehn (*4*) suggested that true immunologic surveillance may take place in the lung, which has a much greater degree of immunologic sensitivity than other sites. However, nonimmunologic factors may be involved in various post-transplant cancers. Bladder cancers were reported in a series

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TABLE 1.—*Observed and expected numbers of cancers and risk ratios for men and women with renal transplants*

Cancer	Males			Females			Total		
	Observed	Expected	Risk ratio	Observed	Expected	Risk ratio	Observed	Expected	Risk ratio
All lymphomas	21	0.966	21.7	12	0.349	34.4	33	1.315	25.1
Hodgkin's disease	0	0.464	0	1	0.139	7.2	1	0.603	1.7
Other lymphomas	21	0.502	41.8	11	0.210	52.4	32	0.712	44.9
Other forms	23	9.383	2.5	14	9.264	1.5	37	18.647	2.0
Large intestine	2	0.796	2.5	0	0.497	0	2	1.293	1.5
Liver and biliary tract	2	0.081	24.7	1	0.014	71.4	3	0.095	31.6
Lung	3	1.603	1.9	2	0.198	10.1	5	1.801	2.8
Breast	—	—	—	2	2.660	0.8	2	2.660	0.8
Cervix	—	—	—	3	2.315	1.3	3	2.315	1.3
Bladder	3	0.556	5.4	0	0.121	0	3	0.677	4.4
Leukemia	3	0.542	5.5	0	0.157	0	3	0.699	4.3
Others	10	5.805	1.7	6	3.302	1.8	16	9.107	1.8
Total person yr		11,161			6,782			17,943	

TABLE 2.—*Observed and expected numbers of cancers and risk ratios according to the interval from first transplant to tumor diagnosis*

Cancers	Interval, yr				
	< 1	1	2	3–4	5+
All lymphomas					
Observed	13	8	7	3	2
Expected	0.57	0.30	0.19	0.18	0.08
Risk ratio	22.9	27.4	37.0	16.9	25.3
Others					
Observed	7	4	8	9	9
Expected	8.38	4.22	2.57	2.40	1.15
Risk ratio	.8	.9	3.1	3.8	7.8

of German transplant recipients for analgesic nephropathy and linked to the same phenacetin-containing drugs that produced the kidney disease (*8*). In our study, however, glomerulonephritis was reported as the condition requiring transplantation in the 3 cases of bladder cancer. In some transplant patients, including those developing leukemia, heavy doses of ionizing radiation were used to prevent rejection. In addition, viruses may trigger the development of some tumors, particularly since papovaviruses and herpesviruses are activated by immunosuppression and are easily detectable in the serum and urine of transplant recipients (*9*).

Latent periods of post-transplant cancer, estimated by the interval between transplantation and cancer onset, may shed light on oncogenic mechanisms. As shown in table 2, the risk of lymphoma increased rapidly within a few months of transplantation and remained at a high level. This trend seems consistent with the concept that post-transplant lymphomas arise from a breakdown of immunosurveillance, with loss of control over cells already initiated and transformed. It is quite unlike the usual pattern for human carcinogenesis in which the latent periods are longer and associated with a risk that increases over time. This pattern seems to apply to other cancers after transplantation, since the increased risk appeared later and increased with length of follow-up. However, the numbers of cases are small, and the trend will be clarified as the survey continues.

Despite case reports of cancers following immunosuppressive therapy for various conditions (*10*), the evidence of elevated cancer risk is not clear-cut. Therefore, the cancers associated with transplantation may result from a combined effect: drug-induced immunosuppression plus immunostimulation by antigens from the grafted organ. However, long-term surveys of various patient groups treated with immunosuppressive drugs are needed to assess fully the hazards of these agents. These studies will not only clarify the mechanisms of cancer susceptibility but will also influence clinical practice. Although the cancer risk involved is currently considered acceptable for renal transplantation, similar risks involved in the use of agents for less serious conditions might be unacceptable.

PRIMARY IMMUNODEFICIENCY SYNDROMES

Since 1951, clinical reports have accumulated on the development of cancer in patients with primary immunodeficiency syndromes, such as sex-linked agammaglobulinemia, severe combined immunodeficiency, Wiskott-Aldrich syndrome, ataxia-telangiectasia, isolated IgA deficiency, isolated IgM deficiency, and common variable immunodeficiency. At the recommendation of the World Health Organization, an international registry was developed to compile data on all patients with these diseases who develop cancer

TABLE 3.—*Summary of neoplasms associated with primary immunodeficiency diseases* [a]

Diseases	Histologic types					
	Epithelial	Lymphoreticular	Leukemia	Mesenchymal	Nervous system	Total
Bruton agammaglobulinemia	0	6	7	0	0	13
Severe combined system	0	7	4	0	0	11
Wiskott-Aldrich syndrome	0	23	3	1	1	28
Ataxia-telangiectasia	8	37	15	1	4	65
IgM deficiency	1	5	0	1	0	7
Variable immunodeficiency	21	26	4	1	1	53
IgA deficiency	10	4	0	2	3	19[b]
Total	40	108	33	6	9	196

[a] Data are taken from (*12*).
[b] Value represents types occurring in 14 individuals.

(*11*). At last report, 196 cases were collected (*12*). More than half of the cancers are lymphomas of various cell types (table 3). The relative frequency of leukemia, particularly the acute lymphocytic type, also is high. These findings are consistent with the predominance of lymphoreticular tumors associated with post-transplant immunosuppression. The number of primary brain tumors in ataxia-telangiectasia also seems high, perhaps linked to the developmental defect involving the brain in this condition. About 20% of the reported tumors are epithelial, but it is unclear if this represents an excess. However, suspicion may be directed to stomach cancer, the tumor most frequently reported among the carcinomas. Despite the fact that in most of the immunodeficiency syndromes death occurs in childhood from infection, it is estimated that cancer has developed in about 7% of patients (*11*). More precise estimates are needed of immunodeficient populations and their risk of developing various forms of cancer.

OTHER IMMUNOLOGIC DISORDERS

Various disorders with "secondary" immunologic defects have been associated with an excess risk of cancer, primarily lymphomas. However, the immune deficiency is varied and complex, often associated with immunostimulation and lymphoid hyperreactivity, and is related to cancer in a manner that seems less precise than with the primary immunodeficiency syndromes. Among 202 patients with nontropical steatorrhea (adult celiac disease), 14 developed lymphomas, including 10 with reticulum cell sarcoma involving the gastrointestinal tract (*13*). In 58 patients with Sjögren's syndrome, reticulum cell sarcoma developed in 3 and Waldenstrom's macroglobulinemia in 1 (*14*). Malaria shares the unusual geographic distribution described for Burkitt's lymphoma in Africa, and the suspected causal relationship is consistent with the capacity of malaria to both depress and stimulate immune mechanisms (*15*). A recent study of 2,554 Danish patients with respiratory sarcoidosis, a multisystem granulomatous disease with marked impairment of cellular immunity and lymphoproliferation, revealed an eleven-fold excess of malignant lymphoma and a three-fold excess of lung cancer (*16*).

Dilantin (diphenylhydantoin) is an anticonvulsant agent that can depress and stimulate immune responses; it occasionally produces lymphoid reactions that usually regress on cessation of anticonvulsant therapy, but sometimes transform into malignant lymphoma (*17*). Of 15 known patients with intestinal lymphangiectasia, characterized by cellular and humoral defects resulting from loss of protein and lymphocytes through dilated intestinal lymphatic channels, 3 developed lymphomas, including 2 involving the gastrointestinal tract (*18*). However, it should be stressed that not all disorders with immune deficiency are clearly prone to lymphoma or other tumors. For example, the risk of cancer is apparently not elevated in leprosy (*19*), a disease with pronounced deficits in cellular immunity, or after thymectomy (*20*), which predisposes to cancer in young laboratory animals.

Since patients with tumors of the reticuloendothelial or lymphoid system may exhibit profound immunologic defects, one wonders about their risk of nonlymphoid tumors. Most often described is the relationship of chronic lymphocytic leukemia (CLL) to skin cancer (*21*). Much less clear is the risk of other cancers. We have preliminary observations from a series of CLL patients reported to the End Results Program that suggest an excess risk of subsequent tumors, particularly melanoma, lung cancer, soft tissue sarcoma, and possibly rectal cancer. Acute leukemia and probably other neoplasms occur excessively following multiple myeloma (*22*) and Hodgkin's disease (*23*), but the contribution of immunosuppression (from disease or treatment)

to the development of the second tumor is difficult to determine.

FAMILIAL NEOPLASIA

Immunologic defects predisposing to cancer may be clinically inapparent, detectable only by laboratory study. A means of identifying subtle mechanisms of susceptibility is afforded by families who are exceptionally prone to cancer. Thus in a sibship aggregation of CLL, we identified defects of cellular and humoral immunity not only in the patients, but also in certain healthy siblings, which led us to believe a subclinical counterpart to the primary immunodeficiency syndromes was present (*24*). Recently, a child of the propositus developed lymphosarcoma, which suggests that the immunodeficiency and susceptibility to lymphoid neoplasms in this family run vertically in the manner of a dominantly inherited syndrome.

Study was made also of a family prone to a wide variety of lymphoproliferative neoplasms; e.g., Waldenstrom's macroglobulinemia (involving a monoclonal elevation of IgM), lymphocytic and histiocytic lymphomas, Hodgkin's disease, and acute lymphocytic leukemia (*25*). In certain healthy members of this family, laboratory studies revealed defects of cellular immunity and polyclonal elevations of IgM. Subsequently, lung adenocarcinoma developed in a family member with these immune defects and in the patient with macroglobulinemia. In a number of recent studies, immunodeficiency has been discovered in families prone to lymphoproliferative neoplasms (*26, 27*).

New developments in the recognition of lymphoid subpopulations by surface markers should help to clarify the mechanisms linking immunogenetic defects to abnormalities of lymphoproliferation. In one family prone to CLL, we found that in 3 of 4 affected siblings the peripheral blood leukemia cells shared δ-heavy and κ-light chains as the only detectable surface immunoglobulin, suggesting an inherited defect in a specific class of lymphocytes (*28*).

We also have studied families prone to nonlymphoid types of cancer, but no solid evidence of defective immunity has been detected except in a kindred prone to stomach cancer (*29*). Because a high frequency of surviving members had impaired lymphocyte transformation associated with antibodies to gastric parietal cells, cellular immune defects and autoimmune mechanisms may be involved in this family's susceptibility to stomach cancer.

AGING

It often has been suggested that the rising incidence of cancer in the later years of life is related to the progressive weakening of immune defenses that occurs with advancing age. However, Doll (*30*) has assembled evidence that age susceptibility to cancer is related less to intrinsic aging mechanisms per se than to the cumulative effect of environmental carcinogens. The issue has been examined in part by studies relating age-at-first exposure to environmentally induced cancer (*30,31*). In some reports, the risk was elevated among people exposed at older ages, such as bladder cancer in dye workers, leukemia following radiotherapy for spondylitis, nasal sinus cancer in nickel refiners, and lung cancer in asbestos workers. Yet in other situations, the risk was greatest in younger people, including various cancers (thyroid, breast, leukemia) in atomic bomb survivors, lung cancer in cigarette smokers, and bladder cancer in occupational groups.

If the age susceptibility to cancer relates in part to defective immunity, one might find evidence of impaired response in individuals destined to develop cancer. This question was approached by a study of cancer risk in persons receiving the tuberculin skin test, an indicator of cellular immunity, as part of a large-scale campaign against tuberculosis in Denmark (*32*). However, no association was found between cancer and the presence or size of the tuberculin reaction.

IMMUNOENHANCING STATES

The surveillance concept indicates not only that weakening of the immune system leads to cancer, but that its strengthening may protect against cancer. Indeed, in experimental animals, stimulation of immune mechanisms by BCG immunization has inhibited the development of cancer. To evaluate this issue in man, Rosenthal et al. (*33*) studied the death records from a group of over 54,000 black children in Chicago who had been vaccinated with BCG soon after birth. The 1 death recorded from leukemia yielded a crude rate of 0.3/100,000/year, which was significantly lower than the published rate of about 2 for leukemia among black children in Chicago. The study was then updated by Crispen (*34*), who reported results on 85,000 vaccinated newborns that suggested protection against all forms of childhood cancer by a factor of about five-fold.

The findings, similar to those of a Canadian study (*35*), led to calls for a clinical trial of BCG vaccination of newborns in the hopes that mortality from childhood cancer might be reduced by as much as 80%.

Since the risk of cancer does not seem unusual among children vaccinated after the neonatal period, this period may be the critical time for inhibiting carcinogenesis by BCG. If so, it is surprising that in certain parts of the world where large numbers of newborns have been vaccinated, no shifts in the incidence of childhood cancer could be detected (*36,37*). Yet the Chicago findings were sufficiently striking to warrant reevaluation. Dr. Crispen provided us with names from vaccination records, which then were matched with names of children recorded in the 1960–69 Childhood Cancer Mortality Registry located at the National Cancer Institute. Thus we could ascertain deaths among children moving from the Chicago area to other parts of the country. In addition, more precise population figures for exposed and unexposed children in Chicago were used, along with a method of analysis that employed person-years of observation. We obtained expected numbers of deaths by multiplying the mortality rate for various cancers for black children in the United States by the person-years of observation in the vaccinated group.

The results have recently been summarized (*38*). The leukemia deaths were about 50% of expectation, whereas the deaths from other cancers were about 40%. These deficits were much less striking than the five-fold protective effect previously reported for all cancers, probably because of analytical refinements and the added mortality data available to us. Although subject to various interpretations, the small magnitude of "protection" against all forms of cancer raises the question of methodologic bias and cannot be used as evidence for recommending either the immunosurveillance theory or BCG vaccination trials.

Another observation may relate to the issue of immunologic reactivity and cancer suppression. A few reports have indicated that the risk of cancer is lower than usual among people with allergies (*39*), who produce excess IgE and may react to new antigens on neoplastic cells through "immediate" hypersensitivity reactions. However, other studies have not confirmed this finding, which remains open to question (*40*).

CONCLUSIONS

The epidemiologic evidence at hand provides little support for the immunosurveillance theory of cancer. Susceptibility to cancer is not uniformly increased by impaired immune responses. Lymphoid neoplasms predominate in various immunodeficient populations; etiologic surveillance mechanisms may be involved in these particular tumors, probably in concert with antigenic stimulation and perhaps other factors, including viruses. The relationships between impaired immunity and lymphoid tumors are intimate and complex, and the pathogenetic sequence is uncertain. Recent observations linking lymphoma to ionizing radiation (*41*) and certain occupational chemicals (*42*) may provide an opportunity to evaluate immunologic mechanisms further. In addition, some epidemiologic studies suggest that failing immunosurveillance may be related to skin cancer (*43*) and to adenocarcinomas of the stomach and lung, although these tumors are not linked to the different immunodeficiency states as pervasively as lymphoid tumors. Continued observations on various immunodeficient populations should help us to define these relationships and to sort out the complex immunologic pathways leading to cancer.

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STUDIES ON MIGRATING POPULATIONS

Nasopharyngeal Carcinoma

International Collaboration on Breast Cancer: Present Status

Current Status of Studies on Colon and Stomach Cancer

Selected Observations on the Epidemiology of Pharyngeal Cancers [1, 2]

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ABSTRACT—The epidemiology of nasopharyngeal cancer (NPC) has been compared with that of other pharyngeal cancers in Los Angeles County. Epstein-Barr virus (EBV) antibody titers were elevated in Caucasians with pharyngeal squamous cell carcinomas regardless of subsite. As expected, an excess of NPC cases was found among Chinese. The role of various etiologic factors in NPC including EBV, inhaled carcinogens, and salted fish was discussed.—Natl Cancer Inst Monogr 47: 129–133, 1977.

Cancer of nasopharynx (NPC) has achieved considerable attention because of the enormously increased rate (10–20/100,000) among the southern Chinese (Kwangtung, Kwangsi, and Fukien Provinces) whether they live in China, the nearby islands of Formosa and Hong Kong, or have migrated to Australia, Hawaii, New York, or California (*1–9*). Although the increased risk of NPC in southern Chinese has been partially ascribed to genetic susceptibility (*2, 10*), an extensive search has been undertaken to find an environmental trigger for NPC. Most studies have focused on the role of inhaled or ingested carcinogens (*1, 2, 11–14, 15*) and the Epstein-Barr virus (EBV) (*16–19*).

Studies of NPC among Chinese have been complicated by the difficulty in separating potential racial genetic factors from environmental agents. This has prompted us to examine the pattern of NPC in non-Chinese as well as Chinese residents of California. In this paper, we report our findings on some aspects of the epidemiology of NPC in comparison with other pharyngeal cancers among Los Angeles County residents. In particular, we report our findings on EBV antibody levels in these patients.

MATERIALS AND METHODS

Data on cases of pharyngeal cancer in 1972 and 1973 were collected from the files of the University of Southern California Cancer Surveillance Program (CSP). The CSP has obtained reports of all microscopically confirmed cancers (excluding skin) reported in Los Angeles County since 1972 (*20*). Cancer sites were coded according to the revised 7th International Classification of Diseases, which codes separately oral pharynx (including tonsils), nasopharynx, and hypopharynx. A fourth classification, pharynx unspecified, was used whenever a subsite of the pharynx could not be established. Selected demographic variables and the pathology report are also included in this analysis. Coding of occupation and industry was done according to methods used in the 1970 census (*21*). A socioeconomic class index from 1 to 5 was assigned to each case; the index was based on the average educational and family income levels of the census tract in which the patient resided (*22*).

Serum samples were collected from patients in each subsite category. Immunofluorescence tests for EBV antigens were performed according to methods previously described (*23*).

RESULTS

Of the 408 cases of pharyngeal cancer collected by the CSP for the 2-year period, 1972 and 1973 (table 1), almost half (48%) arose in the oropharynx. Most (89%) of the cancers, regardless of subsite, were squamous cell carcinomas. This cell type included such other designations as transitional cell carcinomas and lymphoepitheliomas. Other melanomas (2), sarcomas (4), adenocarcinomas (9), and lymphomas (31) comprised the remaining 11%.

The EBV capsid antigen titers are shown in table 2. In whites with squamous cell carcinomas, the virus capsid antigen geometric mean titers (GMT) were only slightly higher for the nasopharynx (GMT=205) than for elsewhere in the pharynx (GMT=158), and both were considerably higher than either nonsquamous cell NPC cases (GMT=32) or control virus capsid antigen results

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TABLE 1.—*Cases of pharyngeal cancer by site and histology, 1972–73*

Tumor type	Site				
	Oropharynx	Nasopharynx	Hypopharynx	Pharynx unspecified	Total No. of cases
Squamous cell carcinoma	169	60	90	43	362
Adenocarcinoma	5	2	2	0	9
Lymphoma	19	9	1	2	31
Rhabdomyosarcoma	1	1	0	0	2
Melanoma	0	2	0	0	2
Malignant tumor (NOS)[a]	1	0	0	1	2
Total	195	74	93	46	408

[a] NOS=not otherwise specified.

TABLE 2.—*EBV titers in cases of carcinoma of the pharynx*

Site	No. of cases	Mean EBV capsid antigen titer	Titers, % ≥160
Nasopharynx (squamous cell)			
White	28	205	75
Chinese	13	417	92
Other pharynx (squamous cell)			
White only	23	158	61
Nasopharynx (other histology)			
White	7	32	14
Controls			
White	88	67	24
Chinese	47	50	4

(GMT=67). The virus capsid antigen GMT of the Chinese NPC cases was higher than that of the whites and Chinese controls. Whether in the nasopharynx or elsewhere in the pharynx, most of the cancers had virus capsid antigen titers greater than or equal to 1:160. These results remain essentially unchanged after they are standardized for age.

Squamous pharyngeal cancer in all subsite categories affected approximately twice as many males as females (table 3). Distribution among the subsites was similar for the different racial groups, except that the 4 Chinese patients had cancer of the nasopharynx.

Table 4 presents the age-specific incidence rates for squamous cell carcinoma of the different sites in the pharynx. The pattern by age group was similar for the different subsites in that incidence rates rose progressively to ages 55–74 and subsequently declined at all subsites. However, the rise from 35 to 44 to 55 to 64 was less for the nasopharynx than for either the oropharynx or

TABLE 3.—*Sex and racial distribution of squamous cell carcinoma of the pharynx*[a]

Racial group	Oropharynx	Nasopharynx	Hypopharynx	Pharynx unspecified	Pharynx total
Caucasian					
Male	93(77)	28(72)	40(66)	21(84)	182(74)
Female	33(64)	15(71)	25(86)	15(83)	88(76)
Black					
Male	14(12)	2(5)	10(16)	2(8)	28(11)
Female	6	2(10)	1(3)	1(6)	10(9)
Mexican American					
Male	4(3)	1(3)	2(3)	2(8)	9(4)
Female	2(4)	1(5)	0	1(6)	4(3)
Chinese					
Male	0	4(10)	0	0	4(2)
Female	0	0	0	0	0(0)
Other Oriental					
Male	0	2(5)	3(5)	0	5(2)
Female	1(2)	1(5)	0	0	2(2)
Race unknown or other					
Male	10(8)	2(5)	6(10)	0	18(7)
Female	6(13)	2(10)	3(10)	1(6)	12(10)
Total					
Male	121	39	61	25	246
Female	48	21	29	18	116
Male : female ratio	2.5	1.9	2.1	1.4	2.1

[a] *Numbers in parentheses* are percentages.

hypopharynx; this slow rise in NPC rates had previously been noted by Buell (*10*). Two cases of NPC occurred in teenagers, but cancers at the other sites occurred only in patients aged 32 or older. One of the teenagers with NPC was of Chinese origin; the other was Caucasian.

Religious preference of patients made no apparent difference in the occurrence of NPC among the subsites (data not shown). Similarly, no striking differences in birthplace were evident among the various groups, except for the Oriental patients with NPC and hypopharyngeal cancer. The mean socioeconomic class of the patients was similar, ranging from a high of 3.2 (nasopharynx) to a low of 3.4 (hypopharynx); an analysis of the occupations of the pharyngeal cancer cases by subsite showed no particular pattern.

DISCUSSION

Much attention has focused on the role of EBV in the pathogenesis of NPC among the Chinese (*15–18*). However, our results show little difference in mean EBV capsid antigen titers among squamous cell carcinoma patients, whether the primary site is in the nasopharynx or elsewhere in the pharyngeal cavity. Moreover, a recent report by Hsu et al. (*24*) showed no difference in

TABLE 4.—*Age-specific annual incidence rates/100,000 cases of squamous cell carcinoma of the pharynx for 1972–73 in Los Angeles County*

Ages, yr	Oro-pharynx	Naso-pharynx	Hypo-pharynx	Pharynx unspecified
0–14	0.00	0.05	0.00	0.00
15–24	0.00	0.00	0.00	0.00
25–34	0.05	0.00	0.00	0.00
35–44	0.47	0.30	0.30	0.06
45–54	2.09	0.99	1.10	0.70
55–64	5.75	1.73	2.52	1.42
65–74	4.93	1.39	3.29	1.14
75+	2.34	0.59	1.56	0.59
Total	1.21	0.43	0.65	0.31

virus capsid antigen results between Taiwanese NPC patients with stage I disease and matched controls. These data support recent studies (*19, 23*) that convincingly demonstrated that the height of the EBV capsid antigen titers in NPC cases is a reflection of tumor mass. The growth of such carcinomas in the pharynx in which EBV is harbored (certainly in lymphoid cells and possibly in epithelial cells) probably accounts for the presence of this virus in NPC tumor tissue and the increase in antibody associated with growth of the tumor (*25–28*).

Several studies have indicated an excess of oropharyngeal and hypopharyngeal cancer among cigarette smokers (*29–31*). However, this association has not been found for NPC (*32*). Moreover, the well-documented increased risk of a second respiratory or upper digestive tract primary cancer among those with a first primary in the same area was not observed for the nasal cavities and nasopharynx (*31*). The age-specific incidence rates of NPC also do not behave like the other cancers associated with cigarette smoking (*10*); in fact, they suggest factor(s) early in life. The recently reported case-control study by Lin et al. (*15*) is difficult to reconcile with other work in this area. In their study of residents of Taiwan, Lin and his associates found (for the first time) a strong association between NPC and cigarette smoking; the risk for heavy smokers was nearly three times higher than for nonsmokers. However, detailed consideration of this paper (*15*) shows that the discrepancy possibly could be due to flaws in the method in which this study was conducted and analyzed.

The Taiwan results were based on a retrospective case-control study in which the cases comprised all new NPC patients in Taiwan over a 1.5-year period; each case was matched by age, sex, and geographic proximity to 3 controls. The results of the interview questionnaire were then analyzed as though these controls were matched for age and sex but otherwise were randomly selected from the population. However, it is unlikely that the selection was truly random; moreover, evidence given in the paper reveals that this assumption is not justified. The invalid assumption could account for the "aberrant" results. A different analysis could check this.

The evidence that militates against randomness is that "single persons had about twice a higher risk (of NPC) than married persons." The authors (*15*) find this risk "difficult to believe," and attempt to explain it by stating that "persons with the disease tend to remain single." This rationale appears extremely unlikely as the cases of NPC are newly diagnosed, and the vast majority of patients are past their twenties. It is much more likely that in the search for controls, the surveyors (daytime interviewing?) missed single men who are at home less. Thus smoking habits correlated with marital status could affect the smoking data.

More important biases might arise from correlations of smoking behavior with place of residence (measuring social class, etc.). The sort of biases we have in mind can be illustrated as follows. Suppose Taiwan has two areas: area A of smokers, where 5,000 Mainlanders and 10,000 Taiwanese live; and area B of nonsmokers, with 10,000 Mainlanders and 5,000 Taiwanese. If the NPC rates are 1% for Mainlanders and 0.3% for Taiwanese, irrespective of area, we then find:

Population	Smokers	Nonsmokers
Taiwanese		
Cases	30	15
Controls	53	38
Mainlanders		
Cases	50	100
Controls	27	77

These data provide relative risks of 1.4 for Taiwanese and Mainlander smokers, even though we generated the data on the hypothesis of a relative risk of 1.

We do not know how much these biases could explain the findings of Lin et al. (*15*), but we think these arguments should be confirmed by analyzing the results more fully, avoiding the biases through an analysis within case-multiple control sets, and taking note of marital status.

The reason for the high incidence rate of NPC among the southern Chinese remains a fascinating question. The decrease in NPC among second and third generation Chinese Americans described by Buell (*33*) and the probable increased

risk of NPC among Caucasians born in southeast Asia (*34*) certainly point to a carcinogen active in the environment of the Chinese. Also, since NPC has been afflicting southern Chinese at a high rate for three-quarters of a century, irrespective of their residence in rural or urban areas (*32*), it would be most sensible to concentrate the search among the Chinese for possible long-standing etiologic factors in their culture.

The search for such an environmental carcinogen has been long and frustrating. Dr. J. H. C. Ho (*2, 32*) suggested that Cantonese salted fish, a source of dimethylnitrosamines, may be an important carcinogen. He pointed out that salted fish is not consumed by northern Chinese, and their rate of NPC is much lower. Salted fish is characteristically given to weanling babies, and exposure to this potential carcinogen at an early age could account for the teenage and early adult cases of NPC. Furthermore, N-dimethylnitrosamines administered sc produced nasal cavity tumors in the European hamster (*35, 36*). Ho proposed that ingested dimethylnitrosamines might produce tumors in man in a specific end organ, e.g., the nasopharynx. In the hamster, more tumors are seen in other parts of the respiratory system (larynx, trachea, lung) as well. The Chinese do not have a similarly increased risk of other respiratory tract cancers. If nitrosamines are etiologically important, they would have to act with exquisite target organ specificity. Further work is needed in this area.

To date, we have little evidence to support the role of inhaled carcinogens. A case-control study of Shanmugaratnam and Higginson (*13*) showed no relationship between the use of snuff or incense and NPC risk. However, the recent study of Lin et al. (*15*) did show a relationship between poorly ventilated living and working areas and NPC risk, but these findings may be subject to the same biases discussed above regarding their results on cigarette smoking.

Industrial factors, such as dust or smoke inhalation, as causative agents of NPC are observed probably as well as or better among the much less NPC-prone non-Chinese populations of this country (Asians, whites, blacks, and Mexican Americans). This is what has prompted our case-control study of NPC in California, which is currently underway.

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Nasopharyngeal Carcinoma: Opportunities for International Collaborative Research in Malaysia and Hawaii [1]

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ABSTRACT—Malaysia and Hawaii have several advantages for epidemiologic and laboratory studies on nasopharyngeal carcinoma. Both have multiethnic populations with different incidence rates of nasopharyngeal carcinoma and different life-styles. Malaysia has large populations of Chinese, Malays, and Indians, and the number of cases of nasopharyngeal carcinoma at any one time is comparatively large. Incidence rates for 1968–72, age-standardized to the World population, for Guangdong hua (Cantonese Chinese) in Malaysia were 24.3/100,000 for males and 12.0/100,000 for females. In Hawaii, the ratio was 12.9/100,000 for males and 6.7/100,000 for females. The small number of cases in Hawaii would require that research in that State be conducted in collaboration with research elsewhere with larger case numbers.—Natl Cancer Inst Monogr 47: 135–141, 1977.

Malaysia, located in the equatorial tropics of Southeast Asia, and Hawaii, on the northern fringe of the tropical Pacific Ocean, represent two distinctly different physical and cultural environments. They do have some features in common, including multiethnic populations with large Chinese components. Among the Chinese of both places the incidence of nasopharyngeal carcinoma (NPC) is high.

MALAYSIA

Malaysia has a special advantage as a place to do research on NPC in that it has large populations of Chinese, Malays, and Indians, each with different incidence rates of the disease. Among the Chinese, NPC is one of the most commonly observed forms, and the number of cases for epidemiologic study is comparatively large.

Malaysia comprises two main areas: Peninsular Malaysia (formerly West Malaysia and before that Malaya), and the Borneo states of Sarawak and Sabah (formerly known as East Malaysia). The population of Peninsular Malaysia is about 10 million. According to the 1970 census (table 1), the ethnic composition (in percent) is: Malays (53), Chinese (35), Indians (11), and others (1).

Malaysia has no population-based cancer registry, but all known cases of NPC since 1968 have been recorded. A special survey was made by the author and a number of Malaysian colleagues to establish a record of all cases between 1968 and 1972 to find incidence rates. This record is maintained by the Department of Pathology at the General Hospital in Kuala Lumpur and is available for general use. Although this record covers the entire country, special efforts in casefinding have been made in the State of Selangor, which includes the capital city, where the opportunity is best for establishing an almost complete record of cases for a major segment of the Malaysian population. Incidence data for Malaysia and for Selangor are given in table 2.

The Malaysian Chinese retain a distinctive pattern of subethnic groups, each with different incidence rates of NPC. Two-thirds of the known cases of this type of carcinoma diagnosed between 1968 and 1972 were in Selangor; their subethnicity was identified. As shown in table 3, estimated incidence rates for the subgroups revealed the pattern of highest rates among Guangdong hua (Cantonese), moderate among Kejia hua (Hakkas), and lowest among Fujian hua (Hokkien).[3] This pattern has been observed in China, Hong Kong, and Singapore.

Hawaii also has a multiethnic population with contrasting incidence rates of NPC; in a total population of 865,000, only a few cases are identified each year. The 1970 population and ethnic proportions are given in table 4. The Chinese comprise about 40,000 now and have by far the highest incidence rate for NPC. People of Hawaiian extraction have the second highest incidence (table 5).

The Hawaiian data were compiled by a population-based tumor registry, and a comparison of figures for 1960–64 and 1968–72 shows that the incidence rate among Chinese has apparently declined during the intervening period. The case

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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[3] The Pin-yin system of transliteration of Chinese names is adopted here because it conforms to the modern Chinese practice of using standard Mandarin rather than dialects such as Cantonese.

TABLE 1.—*Population of Peninsular Malaysia and the State of Selangor, 1970*[a]

Ethnic group	Peninsular Malaysia		Selangor	
	No.	Percent	No.	Percent
Malays	4,685,838	53.2	564,029	34.6
Chinese	3,122,350	35.4	754,348	46.3
Indians	932,629	10.6	298,876	18.3
Others	69,531	0.8	13,454	0.8
Total	8,810,348	100.0	1,630,707	100.0

[a] Figures are based on the 1970 Population and Housing Census of Malaysia.

TABLE 2.—*Incidence of NPC in Peninsular Malaysia and in Selangor, 1968–72*[a]

Ethnic group	Sex	Cases confirmed by histologic examination				
		Peninsular Malaysia		Selangor		
		No.	Crude rate/ 100,000 population/yr	No.	Crude rate/ 100,000 population/yr	Age-adjusted rate/ 100,000 population/yr[b]
Chinese	M	521	6.6	184	9.6	17.3
	F	228	2.9	91	4.9	7.3
Malays	M	66	0.6	21	1.4	2.5
	F	17	0.1	3	0.2	0.3
Indians	M	16	0.6	7	0.9	1.1
	F	4	0.2	1	0.1	—
Others	M	3	1.6	2	5.7	—
	F	4	2.4	3	9.3	—
Total	M	606	2.7	214	5.1	9.5
	F	253	1.1	98	2.5	4.4

[a] Data are based on (*1*).
[b] Values are adjusted to the world standard.

numbers for the other ethnic groups are too small to draw any conclusions. However, the decline in incidence among the Chinese between these two periods may not be a true change. The results of an examination of the case numbers for the 14-year period 1960–73, computed with the use of chi-square to test for deviation from an expected mean number of cases and linear regression for a downward trend, were not significant among either Chinese males or females. Much of the change in rate for Chinese males in table 5 is due to an increasing population denominator, but here room for doubt also exists because of inconsistencies in the declaration of ethnicity from one census to the next. The decade of the sixties coincides with the passing of the second generation of Chinese in Hawaii and the beginning of the passage of the third. If the incidence pattern among Hawaiian Chinese is following that of Californian Chinese, we would expect a decline in rates; however, the present data do not clearly support this.

TABLE 3.—*Estimated incidence of NPC among Chinese and Malay subethnic groups, Selangor, 1968–72*[a]

Subethnic group	Sex	Population, 1970	Crude rate/ 100,000 population/ yr	Age-adjusted rate/ 100,000 population/yr	
				Selangor standard[b]	World standard[c]
Chinese					
Fujian hua and	M	162,811	6.0	7.0	10.0
Chaozhou hua (Hokkien and Teochiu)[d]	F	153,284	1.8	2.0	2.9
Kejia hua	M	95,904	11.3	11.8	18.9
(Hakka)	F	96,271	5.2	5.0	7.1
Guangdong hua	M	89,961	17.1	15.0	24.3
(Cantonese)	F	93,905	9.3	7.9	12.0
Hainan hua	M	18,513	5.5	—	—
(Hainanese)	F	16,454	7.6	—	—
Xinghua hua (Henghua)	F	1,920	—	—	—
Malays					
Malay	M	257,751	0.6		
	F	241,362	0.2		
Indonesian	M	28,692	9.4		
	F	27,934	0.7		

[a] Data are taken from (*1*).
[b] These figures are age-adjusted by the indirect method with the total 1970 Chinese male and female population of Selangor used as standards.
[c] These figures are age-adjusted to the world population.
[d] Fujian hua and Chaozhou hua are combined because they are closely related culturally. In 1970, the Chaozhou hua population in Selangor comprised 26,011 males and 23,921 females. During the 1968–72 period, 6 males and 1 female with NPC were found among the Chaozhou hua.

TABLE 4.—*Population of Hawaii, 1970*[a]

Ethnic group	No.	Percent
Caucasian	254,415	33.1
Chinese	37,751	5.0
Filipino	73,691	9.6
Hawaiian	135,919	17.7
Japanese	208,478	27.1
Black	7,784	1.0
Other	49,756	6.5
Total	767,794	100.0

[a] Data are based on figures from the Hawaii State Department of Health, 1975.

THE HISTORY OF SETTLEMENT

Malaysia and Hawaii have different historical patterns of Chinese settlement, and these underlie some of the modern contrasts. Chinese settlement in Malaysia dates from about 1350 and for the next 300 years was comprised primarily of men from Fujian province (text-fig. 1). Many of these early migrants married Malay women and thus were formed the distinctive communities known as Baba Chinese. By 1800, the Chinese population on the Malay peninsula, excluding Singapore, numbered about 9,000.

TABLE 5.—*Incidence of NPC in Hawaii, 1960–64 and 1968–72*[a]

Sex	Ethnicity	No. of cases		Annual crude rate/100,000 population		Age-adjusted rates/100,000 population			
						Hawaii standard		World standard	
		1960–64	1968–72	1960–64	1968–72	1960–64	1968–72	1960–64	1968–72
Males									
	Caucasian	5	5	0.8	0.7	1.0	0.8		
	Chinese	19	15	19.4	15.5	15.9	11.4	17.1	12.9
	Filipino	9	1	4.1	0.5	2.6	0.3		
	Hawaiian descent	6	8	2.2	2.4	3.3	3.7		
	Japanese	2	7	0.4	1.4	0.4	1.0		
	Other	3	7	4.1	5.8	7.0	11.0		
	Total	44	43	2.5	2.2				
Females									
	Caucasian	1	5	0.2	0.8	0.2	0.9		
	Chinese	8	8	8.6	8.7	6.9	5.5	7.9	6.7
	Filipino	0	0	—	—	—	—		
	Hawaiian descent	1	3	0.4	0.9	0.6	1.3		
	Japanese	2	1	0.4	0.2	0.3	0.1		
	Other	0	4	—	3.1	—	5.9		
	Total	12	21	0.8	1.1				

[a] Data are taken from the Hawaii Tumor Registry, Hawaii State Department of Health; computations are the author's.

After 1825, the influx of Chinese rapidly increased as tin mines and rubber estates were developed and workers were sought. The migrants came first from Fujian province but later from Guangdong and Guanxi (text-fig. 2). Once their work contracts were completed, many Chinese returned to China so that during the period of unrestricted immigration from 1825 to 1929, several million Chinese passed through Malaysia. At the same time, growth of the resident population was steady, except when it was severely interrupted during the Japanese occupation; it now totals over 3.1 million.

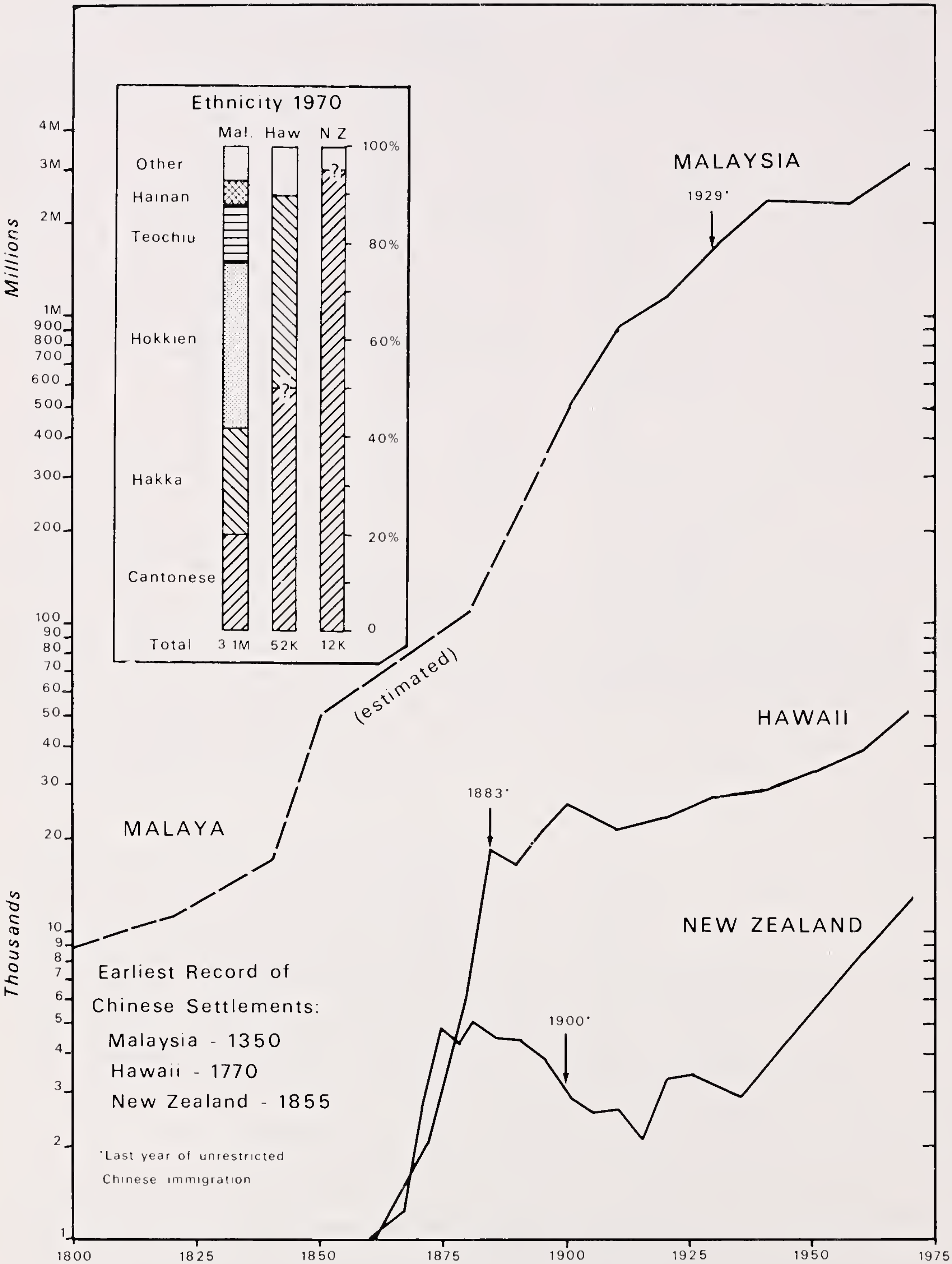
Documentation of marriage patterns is fragmentary but, apparently, intermarriage between Chinese and other ethnic groups was much reduced after 1850. At the same time, few Chinese women migrated to Malaysia so that men returned to China to marry. Beginning about 1920, this situation altered because of the large numbers of females who migrated from China for work on rubber estates. With the consequent adjustment of the sex ratio, the present pattern of little intermarriage among subethnic groups was established.

The largest Chinese subethnic group in Malaysia is the Fujian hua followed by Kejia hua, Guangdong hua, Chaozhou hua (Teochiu), and Hainan hua (Hainanese), and others, all originating from south China (text-fig. 2). These subethnic groups retain strong cultural identities. As a whole, the Chinese in Malaysia contrast even more sharply with Malays, Indians, and other ethnic groups.

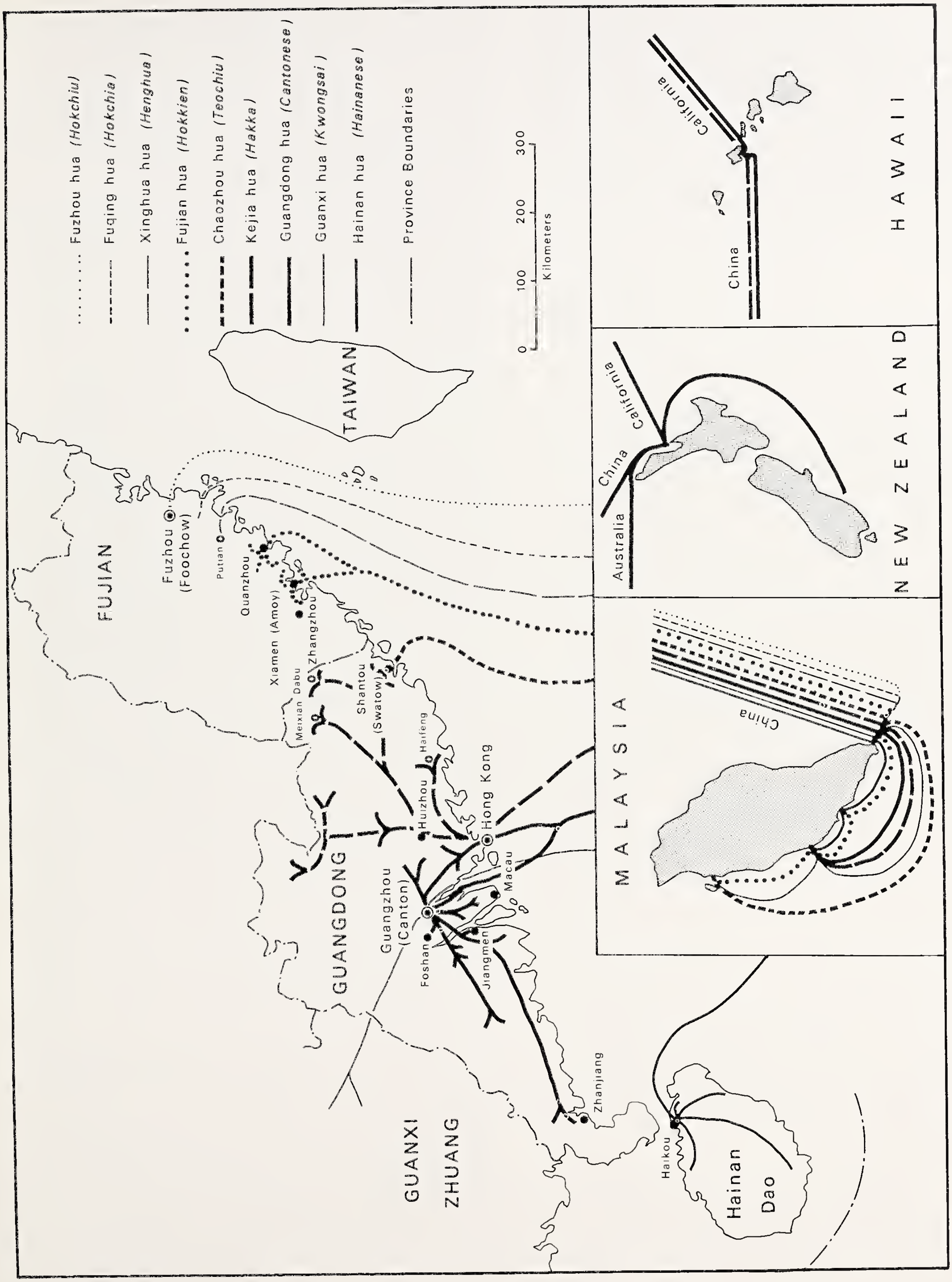
The Chinese settlement of Hawaii was on a much smaller scale. Although a few Chinese were living there in 1770, the main period of immigration was between 1870 and 1900. Restrictions were imposed in 1883. Most migrants were Kejia hua and Guangdong hua from Guangdong province; about two-thirds came directly from China and one-third from California to fulfill labor contracts with the new sugar plantations. They were predominantly young men, many of whom moved again within a few years to China or to North America. Many of those who stayed in Hawaii never married; those who did found Hawaiian, Caucasian, and other non-Chinese partners as often as Chinese. Cultural identity as Chinese slowly became less distinct with the passing of each generation. Cultural adaptation by the Chinese minority to the cosmopolitan ways of the new Hawaii gradually took place.

RESEARCH OPPORTUNITIES

Although certain difficulties in doing research on NPC arise in Malaysia and Hawaii, these areas do afford some special opportunities to explore a number of epidemiologic and pathologic questions. In Malaysia, a large number of new cases are seen each year so that research could be entirely focused on that population (table 2), whereas in Hawaii, the number of new cases



TEXT-FIGURE 1.—Chinese populations, 1800–1975 [(2) and official censuses].



TEXT-FIGURE 2.—Mainstreams of movement of South China subethnic groups to and from Malaysia, New Zealand, and Hawaii, 1800–1929.

annually is too small for most epidemiologic studies. Almost any work contemplated would benefit from a collaborative study (table 5), which could be conducted in Malaysia, Singapore, Hong Kong, Taiwan, California, or other places where a sufficient number of patients with NPC are seen. China is the obvious place for work on this form of carcinoma, and we hope that collaborative studies will be possible in the future.

Research on NPC in Malaysia is made more difficult since no population-based cancer registry or any agency coordinating cancer research is available. Only a small number of people are qualified or interested in cancer research. This generally means that a longer time must be spent in initiating a project; 2 years is minimal for even a modest collaborative effort. Hawaii, on the other hand, has an established registry and the Cancer Center, which serves to communicate and coordinate research activities. It also has well-developed data banks of long standing on ethnic populations that make it easy to select control subjects on an ethnic basis. In terms of general laboratory facilities for cancer research, Malaysia reflects the conditions typical of a developing country as Hawaii does those of a developed country.

Malaysians with interest in cancer research welcome collaborative projects from other countries because of the opportunity afforded them for additional expertise and resources and a better chance to do research. Because of local pressure of routine professional work, limited resources, and more urgent communicable disease problems, little substantive research on cancer in general has ever been undertaken. For Hawaii, the main advantage in collaborative work is the means to increase the numbers of cases sufficient for valid research designs.

Some of the types of research that would benefit from investigations in Malaysia or Hawaii are:

1) Genetic studies are needed, especially in Malaysia. Such studies as associations between the histocompatibility leukocyte antigen (HLA) genetic system and NPC could be done among sizable populations of distinct ethnic groups with different incidence rates of the disease. Similar studies would be practical in Hawaii if each one was part of a larger study.

2) Much could be learned from comparative ethnocultural studies in Malaysia and Hawaii. In Malaysia, distinctive cultural differences persist among ethnic and subethnic groups. To test a hypothesis that a genetic susceptibility is a strong precondition to the action of environmental carcinogenesis, one could establish comparative retrospective or prospective studies among populations having different genetic backgrounds and behavioral patterns. Comparisons of patients from generally low-risk populations (such as Caucasians, Malays, and Filipinos) with patients from generally high-risk populations (Chinese) could also be feasible.

3) Ancestral contrasts are also possible in Malaysia. Among the patients with NPC in the Selangor study, one-third were born in China, another third in Malaysia of Chinese parentage, and one-third had longer ancestral association with Malaysia. Whereas the crude incidence rates presently do not suggest that place of birth influences determination of risk of NPC, careful study of age-specific rates over the next two decades may be more revealing. The opportunity is here to examine hypotheses concerning the role of cultural adaptation in the etiology of the disease through group and generation differences and contrasts between old and new migrants.

4) Specific associations between environmental factors and NPC could be examined in Malaysia and Hawaii with the use of comparative ethnic population groups. It should be possible in the near future to identify genetic subgroups within groups of patients and normal controls on the basis of the HLA genetic system (*3*). Given that the response of genetic subgroups to environmental carcinogens may vary between subgroups, considerable improvement in case-control studies of environmental associations with NPC would be possible if the subgroups can be identified.

5) Pathologic and anatomic studies of the nasopharynx are feasible in Malaysia where facilities for autopsy and numbers of cases are favorable.

For all kinds of studies, researchers in Malaysia have the advantage of making comparisons between groups in whom the risk of NPC is high and in those in whom it is low. Enough cases can be located among low-risk groups to make meaningful comparisons, and it may well be more rewarding to concentrate on these low-risk groups because etiologic factors may reveal themselves more clearly than they would in the high-risk groups.

Much might be gained from joint studies in Malaysia and Hawaii and in other places where epidemiologic work on NPC is practical. A certain degree of collaboration has already been achieved between studies in Hong Kong, Singapore, and Malaysia through the International Agency for Research on Cancer, e.g., by the use of the same

questions in interviews and the same forms for data analysis.

CURRENT WORK

In Malaysia, two recent projects have been concerned with NPC. The first involved the World Health Organization Immunology Research and Training Centre in Singapore (affiliated with the International Agency for Research on Cancer, Lyon), the University of Malaya, and the Institute of Radiotherapy and Nuclear Medicine at the General Hospital, Kuala Lumpur. This team of scientists obtained samples of blood from Chinese patients with NPC and interviews that included medical, occupational, and residential histories. Blood analysis for HLA typing was the chief concern of the Singapore group, and the interview data were of more interest to the Malaysians. This collaborative program terminated in mid-1974.

The second study involved the International Center for Medical Research, University of California at San Francisco, and the Institute for Medical Research in Kuala Lumpur. Collaboration was also arranged with the International Agency for Research on Cancer in Lyon. This project, in which workers established the incidence rates mentioned earlier and conducted a retrospective study of the specific environments of groups of cases and controls, has been completed and is in process of publication. No major research activities concerning NPC in Malaysia are being conducted at the present time.

The same is true for Hawaii: No research activities in progress directly relate to NPC. I plan to begin a preliminary study that will include interviews of patients and their families to establish ancestral, occupational, and residential histories; I will also review their medical histories. An extension of this work into a collaborative study dealing with specific environments of case and control groups would provide more useful information.

CONCLUSION

Without doubt, collaborative research involving contrasting populations, environments, and incidence rates of NPC offers the best way of finding solutions to some of the basic questions about the epidemiology of the disease. Until recently, NPC was studied with few cases in fairly homogeneous populations and environments. However, the opportunity for making collaborative studies on contrasting groups in Malaysia or Hawaii may soon pass as the contrasts themselves fade with more intermarriage and cultural mixing.

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Histocompatibility Leukocyte Antigen Patterns and Nasopharyngeal Carcinoma [1]

M. J. Simons [2] *and* N. E. Day [3]

ABSTRACT—Incidence patterns indicated the prominent role of genetic factors in this type of cancer. A histocompatibility leukocyte antigen (HLA) profile of *A2* and a *B*-locus antigen, Singapore 2 (Sin 2), was identified. An association between these genes and increased risk for nasopharyngeal carcinoma (NPC), was confirmed. The risk was restricted to the "co-occurrence" of *A2*, *B-Sin 2*, suggesting that the genotype predisposing to the development of NPC was the *A*, *B-Sin 2* haplotype. Similar associations were found to exist in Malaysian and Hong Kong Chinese so the *A2*, *B-Sin 2* phenotype is a feature common to Asian Chinese in at least three locations. Preliminary HLA studies of medium NPC incidence in Tunisians and Malays indicated that patients with NPC of both ethnic types have altered HLA antigen profiles. If the findings of a locus-*B* antigen deficit in Tunisians and the role of A9 with *B*-locus antigens in Malays can be confirmed and clarified, the histocompatibility genetic hypothesis of NPC predisposition would be substantially strengthened.—Natl Cancer Inst Monogr 47: 143–146, 1977.

The high incidence of NPC among Chinese and Chinese-related peoples compared with that of Caucasian and most other populations in the world has given rise to the hypothesis that a prominent genetic element is involved in susceptibility to this type of cancer. Since the genetic bases of some forms of inherited variation in disease susceptibility may be expressed through immunogenetic systems, it was considered worthwhile to study the histocompatibility leukocyte antigen (HLA) type of nasopharyngeal carcinoma (NPC) patients. The first small study of only 28 NPC-positive patients and 27 NPC-negative controls (clinically suspected of having NPC, but with no histologic evidence of cancer) revealed a difference in the HLA profile. The patients had an increased frequency of undetectable antigen(s) at what is now termed locus *B*. This finding of a relatively larger locus-*B* blank in the patients with NPC was confirmed in a larger study of 144 of these patients and 61 NPC-negative controls (*1*). In this second study, an increased frequency of the locus-*A* allele *HLA–A2* was also observed. We hypothesized that the higher risk associated with the locus-*B* blank reflected the presence of further HLA antigen(s), undetected by the antisera used that were largely of Caucasian origin, and that this antigen would be associated with a high risk for NPC and found mainly in Chinese-related populations.

To explore this hypothesis, sera from about 500 pregnant Chinese women were screened against lymphocytes from NPC patients and NPC-negative controls. An activity was identified that occurred only with a locus-*B* blank, was more common in patients with NPC than in the controls, and which segregated in families with HLA haplotypes (*2*). This activity, provisionally designated Singapore 2 (Sin 2), corresponded to a hitherto unidentified locus *B* antigen and was independently confirmed in the United States (*3*).

The most recent study of 110 Singapore Chinese patients with NPC and 91 NPC-negative controls (*4*) confirmed the association between increased risk for NPC and the HLA genes *HLA–A2* and *Sin 2*. The risk was restricted to the "co-occurrence" of *A2–Sin 2*, suggesting that the genotype predisposing to development of NPC was the *A2–Sin 2* haplotype. In an earlier paper at this meeting (*5*), evidence was presented that a similar association existed in Malaysian and Hong Kong Chinese. The findings indicated that the increased risk for NPC associated with the *A2–Sin 2* phenotype was a feature common to Asian Chinese in at least three geographic locations.

Dr. B. E. Henderson confirmed the increased frequency of A2-blank antigen in American Chinese NPC patients. The Sin 2/Hsieh (HS) antigen has a frequency of 25% in normal American Chinese, and Dr. Paul Terasaki found the gene in a few American Chinese patients with NPC (personal communication). Whether the locus-*B* blank among the American Chinese NPC cases will be substantially filled by the *Sin 2* gene has yet to be determined. Nonetheless, it seems likely that the HLA pattern of *A2–Sin 2* will be associated with an increased risk for NPC in Asian and American Chinese.

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[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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THE SIGNIFICANCE OF HLA-ASSOCIATED DISEASE SUSCEPTIBILITY GENES

The hypothesis we wish to propose here is that the high risk for NPC found among the Southern Chinese has a genetic basis mediated by alleles of the HLA system.

Mongoloid groups are the only populations in which *Sin 2* has been observed. Among Mongoloid groups, only in the Chinese has a disequilibrium been observed between *A2* and *Sin 2*. Thus as the haplotype *A2–Sin 2* is the genotype of the *A* and *B* loci associated with high risk for NPC, we can speculate that the particularly Chinese disequilibrium between *A2–Sin 2* is a major factor in their increased risk for the disease. The two reasons that the haplotype *A2–Sin 2* is not itself the major Chinese factor associated with NPC are: 1) With an associated relative risk of only 2.3 and a frequency of about 25% among Cantonese, only 25% of the NPC risk among Cantonese is attributable to the haplotype; 2) over half the Chinese NPC cases do not have *A2–Sin 2*. Rather than postulate a further genotype of a system unrelated to HLA, it is simpler to hypothesize the existence of a *NPC disease susceptibility* (*DS*) gene in linkage disequilibrium with *A2–Sin 2*, which carries a high risk for NPC and is found predominantly among the Southern Chinese. That is, *A2–Sin 2* is part of a sequence of alleles preferentially preserved among the Southern Chinese, another part of which is associated with high risk for NPC. Thus in this context, it is likely that the *A2–Sin 2* haplotype will only be associated with increased risk for NPC in those ethnic groups among whom *A2–Sin 2* both occur and show linkage disequilibrium.

Only for Chinese has this precondition been established. On this reasoning it follows that no association is likely to exist between the frequencies of *A2* and/or *Sin 2* and NPC. In the Japanese, for example, the gene frequency of *Sin 2* is almost half that in Chinese (approximately 7%) but there appears to be no linkage disequilibrium with *A2*. The incidence of NPC is low in the Japanese. Even among ethnic groups with medium NPC incidence there is no reason to expect an association with the specific alleles *A2* and *Sin 2*. Malays and Tunisians are two such medium NPC-incidence peoples. They are of particular importance in immunogenetic studies of NPC, since Malays have a history of genetic admixture with Mongoloid peoples, whereas Tunisians are a mixed population of Maghrebian type, with no known appreciable association with Mongoloid genes. Although no association is necessarily expected between *A2* or *Sin 2* and NPC in either Tunisians or Malays, the hypothesis of a single *NPC-DS* locus allele common to most, if not all, patients with NPC does imply a relationship between frequency of that allele and the incidence of NPC in the ethnic group.

There is no reason to suppose that the *DS* 'gene' is coded at one locus. In view of the existing disequilibria among alleles at loci *A*, *B*, and *D*, which indicate the functional importance of a sequence of alleles as a series, one would propose that the *DS* gene consists of a sequence of alleles at different loci, preserved in disequilibrium by their functional advantage as a sequence. In this way, the frequency of the *DS* gene would be closely related to the degree of disease associated with HLA antigens and to the strength of the disequilibrium among the HLA antigens forming part of the preserved sequence. Among Chinese with the highest incidence, linkage extends even to alleles of HLA locus *A*. In Caucasians who show a low incidence, there may be no disequilibrium even with alleles of the most centromeric of the HLA loci, that of locus *D*. In Malays and Tunisians (medium incidence), linkage may exist with HLA genes other than the haplotype *A2–Sin2* to produce an HLA profile associated with a risk for NPC. Do the results of HLA typing of these two populations reveal any alteration of HLA pattern?

HLA PATTERNS IN TUNISIANS

Betuel and colleagues (5) studied 193 Tunisian subjects, including 109 with NPC. Among the NPC patients, *A2* occurred less often (29%) than among the controls (42%), and *Sin 2* was not observed once. An appreciably higher frequency of a second-locus blank was found among the NPC cases (46% against 37%); however, the statistical significance attained was only marginal. When the second-locus phenotypes were examined in detail, considerable differences appeared between the cases and the controls. Although the study was inconclusive, results were consistent with an altered HLA profile among the Tunisian patients with NPC.

HLA PATTERNS IN MALAYS

The first study of 104 Malays was completed in 1971. At that time, HLA-typing antisera were available only for 6 alleles at locus *A* and 11 alleles at locus *B*. The gene frequency (GF) blank

at both loci was large (31.6% and 19.3%, respectively), but clear evidence for heterogeneity restriction of the detectable alleles was obtained. Overall, the pattern resembled that of Chinese, in that *A1*, *A3*, *A10*, *A7*, and *A8* occurred with low frequency, but the frequency of common genes differed markedly. For example, *A2* and *A11* had GF's of 15.6 and 11.7% in Malays, whereas in Chinese, the corresponding frequencies were 28.3 and 28.8%.

Sin 2 occurs with extremely low frequency in Malays (approximately 3%), and in a study of 40 Malay NPC patients, *Sin 2* was not detected. Thus *Sin 2* is not a component of any HLA type associated with NPC in Malays. At locus *A*, the GF of *A9* was extremely high (47%), whereas the GF for *A2* was only 9%. In comparison, normal subjects have a GF of 16%. At locus *B*, *BW15* (GF, 15%) and *B18* (GF, 16%) were the most frequent alleles. The haplotype *A9–BW15* had a delta value (Δ) for linkage disequilibrium of 0.003; i.e., no linkage between the two alleles. In marked contrast, Δ for *A9–B18* was 0.061, reflecting a strong linkage. All *B18*-positive patients also had *A9*. The linkage disequilibrium of this haplotype in Malay NPC patients is of the same order as that of *A2–Sin 2* in normal Chinese (Δ=0.054). Unfortunately, no information is available as to whether this haplotype has a positive Δ in normal Malays. If studies in progress reveal linkage disequilibrium of *A9–B18* in normal Malays and if the preliminary finding in Malay NPC patients can be confirmed, the histocompatibility genetic hypothesis of NPC predisposition would be substantially strengthened.

FURTHER CHARACTERIZATION OF THE *A2–SIN 2* CHINESE HAPLOTYPE

It is agreed that the linear sequence of the 4 HLA loci is locus *A*, *C*, *B*, and *D*, with locus *D* located nearest the centromere. Payne (*6*) has shown that *CW1/CW3* is strongly linked to both *HLA–A2* and *HS* (*Sin 2*). We have focused attention on locus *D* for two reasons (*7*): The relative NPC risk associated with *Sin 2* is greater than that with *A2*. This finding suggests that the putative *NPC-DS* locus is chromosomally located on the locus-*D* side of locus *B*. Second, the HLA region in man is structurally homologous with major histocompatibility complex (MHC) regions in mice and nonhuman primates. In these species, most of the MHC-linked immune response (IR) genes are located in the chromosomal region bearing the major locus controlling allogeneic lymphocyte interactions that occur in mixed lymphocyte cultures (MLC). If the *NPC-DS* locus is, or is linked with, an IR gene and the HLA fine structural homology exists to the extent that many IR genes are located in the locus-*D* region, then it is likely that a locus *D* allele linked with *Sin 2* will be associated with a relative risk for NPC higher than the twofold or threefold of *Sin 2*.

Individuals who appear to be homozygous for such a locus-*D* allele, designated *Singapore 2a* (*Sin 2a*), have been identified. Preliminary results of MLC-typing of NPC patients do suggest that the risk associated with *Sin 2a* may indeed be higher than with *Sin 2*.

The molecular, biologic, and immunovirologic evidence for an intimate association between the herpes group virus, Epstein-Barr virus (EBV), and NPC is compelling. The belief that EBV has an oncogenic role in NPC varies greatly among scientists. Dr. Henderson has reported that, in American patients, high levels of antibodies to EBV are phenomena shared by NPC and several types of oropharyngeal carcinomata. Among Singapore Chinese patients, the association between high EBV antibody levels appears to be confined to NPC patients. Furthermore, in a survey of serum antibodies to a range of herpes group viruses (HSVI, HSVII, CMV, and VZ) and other viruses, only with EBV was there a difference between Singapore Chinese NPC patients and the comparison group.

The availability of a genetic marker for NPC risk allows examination of the role of EBV in several ways. One approach is to determine whether altered immunoresponsiveness to EBV "cosegregates" with the NPC-risk haplotype among family members of NPC patients. The EBV is conveniently ubiquitous, since virtually all residents of Singapore over 10 years of age have been exposed and, therefore, lack of exposure will presumably not complicate analysis of the immune status of family members. A major problem is to decide which parameters of immunity to use; also, we must consider immunity to specific antigens. Although EBV is ubiquitous, NPC is relatively rare. Perhaps the HLA-associated immunodeficiency is not related to the response to EBV per se but with immune responses to neoantigens arising as a consequence of EBV infection. These possibilities will have to be given close consideration before a battery of tests is instituted that purport to survey relevant parameters of immune responsiveness. In principle, the "cosegregation" type of study is a powerful approach to clarifying the role of EBV. Its potential will

probably only be realized when techniques have been developed to measure qualitative as well as quantitative aspects of immune responsiveness.

CHROMOSOME NUMBER 6 AND INCREASED SUSCEPTIBILITY

The HLA genes associated with increased susceptibility to NPC are part of the gene system, localized to autosomal chromosome number 6. Thus the HLA-associated risk can be expected to be distributed equally among males and females. Yet NPC has a male:female sex ratio of approximately 2.5:1. Clearly, factors other than HLA-linked genes that influence the occurrence of NPC exist, but those responsible for the differential sex incidence are not yet understood.

Several diseases show an HLA association and a sex difference in incidence. The best example is ankylosing spondylitis in which there has been a strong association with *B27* in male and female patients; yet the disease has a male:female sex ratio of approximately 10:1. Thus it is a mistake to infer from the differential sex incidence in NPC that HLA-linked *NPC-DS* genes are not important predisposing factors or of equal significance in males and females.

WHY IS THE NASOPHARYNX INVOLVED?

Because carcinoma develops in the nasopharynx, some factor or factors must have what might be called a nasopharyngotropic action. If EBV is an oncogenic agent, the fact that viral excretion occurs in the upper pharynx may define the anatomical region of the target. Localization to the nasopharynx may reflect cell proliferative characteristics at the junction of two cell types. Alternatively, exposure to environmental carcinogens may have a selective or differential effect on the nasopharynx, promoting the development of malignant change in a predisposed person. Such a role has been proposed for nitrosamines produced by the action of bacteria on a variety of ingested foods. In this context, Dr. J. H. C. Ho attributes great importance to dietary habits that include the eating of salted fish. Whatever the mechanism proves to be, any discussion of the etiopathogenesis of NPC and any consideration of the role of the genetic factors, must include the question, "Why is the nasopharynx involved?"

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Immunogenetic Aspects of Nasopharyngeal Carcinoma. V. Confirmation of a Chinese-Related HLA Profile (A2, Singapore 2) Associated With an Increased Risk in Chinese for Nasopharyngeal Carcinoma[1,2]

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ABSTRACT—*Histocompatibility locus A* typing of 43 Malaysian Chinese and 51 Hong Kong Chinese patients with nasopharyngeal carcinoma (NPC) confirmed the association between the occurrence of *A2–Sin 2* and the increased risk for NPC that was previously demonstrated in Singapore Chinese. The results support the previous interpretation that the *histocompatibility locus A* genotype of importance in NPC predisposition is the *A2–Sin 2* haplotype. The *histocompatibility locus A*-linked, genetically determined NPC risk is common to Asian Chinese from at least three geographic locations.—Natl Cancer Inst Monogr 47: 147–151, 1977.

Present knowledge of the fine structure of the *histocompatibility locus A* supergene, schematically diagrammed in text-figure 1, was outlined by Dr. Terasaki (*1*) in the previous paper. Among the alleles of locus *B* (*2*) is one that we designated *Singapore 2* (*Sin 2*). The finding that *Sin 2* was a genuine locus *B* allele was independently confirmed by Payne and her colleagues (*3*) when they described a new *histocompatibility locus A* activity called *Hsieh* (*HS*). Exchange of sera established that *Sin 2* and *HS* were operationally identical alleles. The *Sin 2* specificity has not yet been assigned a number within the *B* locus by the World Health Organization, *Histocompatibility locus A* Nomenclature Committee. Text-figure 1 shows the *Sin 2* specificity and previous designations of other *histocompatibility locus A* specificities in parentheses.

In our report (*2*) of the identification of *Sin 2*, we provided preliminary evidence of an association between the occurrence of *Sin 2* and NPC among Chinese. Recently, we completed a study of 110 Singapore Chinese patients with NPC and 91 control subjects. (*4*). The increased frequency of *Sin 2* among NPC positives (40% compared with 25.3%) was statistically significant ($P = 0.014$; relative risk = 1.97). The increased risk for NPC in Chinese was confined to the joint occurrence of *Sin 2* with the locus *A* allele, *A2*; the occurrence of either *Sin 2* or *A2* without the other did not increase the risk. These results indicated that the risk for developing NPC increased only when the genes coded for *A2* and *Sin 2* were on the same chromosome. Thus the genotype of importance was the *A2–Sin 2* haplotype.

Another finding of this study emerged when the frequencies of the "co-occurrence" of *A2* and *Sin 2* were analyzed among NPC-positive and control subjects according to dialect group. For the controls, the frequency of *A2–Sin 2* was 26.7% among Cantonese but only 11.6% among Hokkiens and Teochews. This difference is of particular interest since the incidence of NPC shows a similar twofold difference in the same direction (*5*).

This paper reports results from studies of 43 Malaysians and 51 Hong Kong Chinese patients with NPC. The association between *A2–Sin 2* and the increased risk for NPC experienced by the Chinese are described. Data from research on Singapore patients are included to provide a comprehensive account of the present status of *histocompatibility locus A* studies among Asian Chinese patients with NPC (*4*).

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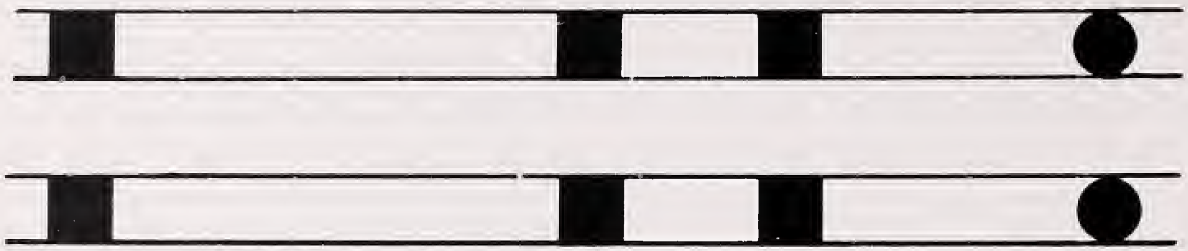
(CHROMOSOME 6)



(LA, 1ST, SD1)	(3RD, SD3)	(FOUR, 2ND, SD2)	(MLR, LD1)
A	C	B	D
A1 (A1)	CW1 (T1)	B5 (A5)	DW1 (LD101)
A2 (A2)	CW2 (T2)	B7 (A7)	DW2 (LD102)
A3 (A3)	CW3 (T3)	B8 (A8)	DW3 (LD103)
A9 (A9)	CW4 (T4)	B12 (A12)	DW4 (LD104)
A10 (A10)	CW5 (T5)	B13 (A13)	DW5 (LD105)
A11 (A11)		B14 (W14)	DW6 (LD106)
A28 (W28)		B18 (W18)	
A29 (W29)		B27 (W27)	
AW23 (W23)		BW15 (W15)	
AW24 (W24)		BW16 (W16)	
AW25 (W25)		BW17 (W17)	
AW26 (W26)		BW21 (W21)	
AW30 (W30)		BW22 (W22)	
AW31 (W31)		BW35 (W5)	
AW32 (W32)		BW37 (TY)	
AW33 (W19.6)		BW38 (W16.1)	
AW34 (MALAY 2)		BW39 (W16.2)	
AW36 (MO*)		BW40 (W10)	
AW43 (BK)		BW41 (SABELL)	
		BW42 (MWA)	
		(SIN 2, HSIEH)	

TEXT-FIGURE 1.—*Histocompatibility locus A* supergene.

MATERIALS AND METHODS

The 110 Singapore Chinese and 43 Malaysian Chinese patients who were selected at random had a clinical diagnosis of NPC confirmed by histologic evidence of carcinoma. Ninety-one Singapore Chinese who were suspected on clinical grounds of having NPC, but in whom no evidence of cancer was seen in histologic preparations of biopsy tissue served as controls (NPC negative). The *histocompatibility locus A* study of these NPC-positive and -negative subjects has been completed (*4*). The studies of the patients from Hong Kong were concerned with the *histocompatibility locus A* genotype of young patients (less than 25 years at diagnosis) and of those from families with multiple NPC cases. Since these family studies are still in progress (November 1975), only the *histocompatibility locus A* phenotype data of 18 young patients and of 33 multiple NPC-case family patients are described. The methods of lymphocyte separation and *histocompatibility locus-A* typing were reported elsewhere (*4, 6*).

RESULTS

Details of the *histocompatibility locus A* antigen and gene frequencies in the Singapore and Malaysian Chinese with NPC are shown in table 1. Most of the genes were detected with the blank at the locus *A* ranging from 1.6 to 5.5% and that at locus *B* from 2.5 to 5.8%. The frequencies of "blank" antigens at both loci were high, which indicated the common occurrence of homozygosity. This was expected in view of the restriction of *histocompatibility locus A* heterogeneity among Chinese, with 10 of the 24 antigens showing a frequency of less than 5%. The overall gene frequency patterns were similar, although small differences were observed that involved the "*W19*" group of specificities, *A13* and *W22*. The statistical significance of these differences disappeared with correction for the number of specificities under test.

The frequencies of both *A2* and *Sin 2* in the 2 groups were similar. Table 2 shows in more detail the frequencies of the joint occurrence of *A2* and *Sin 2*. Since the minimum difference between the 2 groups was not significant, it was statistically permissible to pool the data. In table 3, the *histocompatibility locus A* antigen and gene frequencies of the combined 153 NPC patients were compared with those from 91 Singapore Chinese controls. At locus *A*, the higher gene frequency of *A2* in the patients (39.5 vs. 30.4%) was compensated for by a decrease in *A11* gene frequency (25.4 vs. 36.2%). Among patients with NPC, several genes show at locus *B*, a marginally decreased frequency in compensation for the increased frequency of *Sin 2* (21.7 vs. 13.6%).

Of the 43 Malaysian NPC patients typed for *Sin 2*, 27 were Cantonese and 16 were Hokkiens or Teochews. The joint occurrence of *A2–Sin 2* in these 2 dialect groups (33 and 25%, respectively) was not statistically different from that in the corresponding Singapore groups (39 and 35%). In table 4, the pooled data for the NPC patients were compared with those of the NPC-negative controls. Among the NPC-positive patients, no

TABLE 1.—*HLA antigen and gene frequencies in Singapore and Malaysian Chinese patients with NPC*

Antigen	Singapore Chinese[a] Frequency, %		Malaysian Chinese[b] Frequency, %	
	Antigen	Gene	Antigen	Gene
A 1	0.9	0.0045	0	0
A 2	60.0	0.3675	72.1	0.4118
A 3	1.8	0.0090	0	0
A 9	37.3		25.6	0.1375
A10	6.4	0.0325	16.3	0.0852
A11	45.5	0.2618	41.9	0.2378
W19	19.1	0.1006	14.0	0.0727
Blank	29.1	0.0159	38.0	0.0550
A 5	13.6	0.0705	16.3	0.0852
A 7	1.8	0.0090	2.3	0.0116
A 8	1.8	0.0090	0	0
A12	2.7	0.0136	2.3	0.0116
A13	17.3	0.0906	9.3	0.0477
W 5	6.4	0.0325	7.0	0.0357
W10	35.5	0.1969	34.9	0.1932
W14	0	0	0	0
W15	20.9	0.1106	23.3	0.1243
W16	11.8	0.0609	9.3	0.0477
W17	21.8	0.1157	16.3	0.0852
W18	1.8	0.0090	0	0
W21	0	0	4.6	0.0233
W22	4.5	0.0228	11.6	0.0598
W27	0.9	0.0045	4.6	0.0233
TY	0.9	0.0045	0	0
Sin 2	40.0	0.2254	34.9	0.1932
Blank	18.0	0.0245	43.7	0.0582

[a] No. of patients = 110.
[b] No. of patients = 43.

TABLE 2.—*Joint occurrence of* HLA–A2 *and* Sin 2 *among Singapore and Malaysian Chinese NPC patients*

Antigen	*Sin 2*	Non-*Sin 2*	Total
Singapore[a]			
HLA–A2	39	27	66
Non-HLA–A2	5	39	44
Total	44	66	110
Malaysian[b]			
HLA–A2	13	18	31
Non-HLA–A2	2	10	12
Total	15	28	43

[a] Frequency of A2-Sin 2 = 35.5%.
[b] Frequency of A2-Sin 2 = 30.2%.
$\chi^2 = 0.38$ (not significantly different).

TABLE 3.—*HLA antigen and gene frequencies in Chinese NPC-positive and -negative subjects*[a]

Antigen	NPC positive		NPC negative	
	Frequency, %		Frequency, %	
	Antigen	Gene	Antigen	Gene
A 1	0.7	0.0036	1.1	0.0055
A 2	63.4	0.3951	51.6	0.3043
A 3	1.3	0.0066	2.2	0.0111
A 9	34.0	0.1876	35.2	0.1950
A10	9.2	0.0472	11.0	0.0566
A11	44.4	0.2544	59.3	0.3620
"W19"	17.6	0.0923	13.2	0.0683
Blank	32.6	0.0132	26.7	0
Total		1.0000		1.0028
A 5	14.4	0.0748	11.0	0.0566
A 7	2.0	0.0011	3.3	0.0166
A 8	1.3	0.0066	0	0
A12	2.6	0.0014	2.2	0.0111
A13	15.0	0.0781	15.4	0.0802
W 5	6.5	0.0331	7.8	0.0398
W10	35.3	0.1957	38.5	0.2158
W14	0	0	0	0
W15	21.6	0.1146	24.2	0.1294
W16	11.1	0.0572	13.2	0.0683
W17	20.3	0.1073	26.7	0.1438
W18	1.3	0.0066	1.1	0.0055
W21	1.3	0.0066	0	0
W22	6.5	0.0331	11.0	0.0566
W27	2.0	0.0011	6.7	0.0341
TY	0.7	0.0036	1.1	0.0055
Sin 2	38.6	0.2165	25.3	0.1357
Blank	28.2	0.0692	13.3	0.0010
Total		1.0000		1.0000

[a] Of the 153 NPC-positive subjects, 110 were Singapore Chinese and 43 were Malaysian Chinese; 91 patients were NPC negative.

apparent difference was found among the frequencies of *A2–Sin 2* according to dialect group. The frequency of 34.6% in the total number of Chinese NPC-positive patients was significantly higher ($P<0.01$; relative risk = 2.4) than that in the comparison subjects (17.8%).

Eighteen Hong Kong patients with NPC who were less than 25 years of age at the time of diagnosis were typed for *histocompatibility locus A*. *A2* was present in 11 (61%). *Sin 2*–typing reagents were not available when the first 5 patients were studied. Four of the last 13 had *Sin 2* (31%) and also *A2*.

Of the 33 NPC patients typed as part of the ongoing multiple NPC case family studies, 26 (79%) were A2 positive. *Sin 2* was detected in 14 (42%) of the 33, and all 14 were also A2 positive. The *A2–Sin 2* joint occurrence frequency of 42% was slightly higher than that found in Singapore and Malaysian patients with NPC.

DISCUSSION

The possibility of an association between *Sin 2* and risk for NPC was raised in the paper describing the new locus *B* allele (*2*). Results of a study of 110 Singapore Chinese with NPC and 91 controls supported the existence of an association (*4*). *Sin 2* was present in 44 (40%) patients and in 28 (25.3%) of the controls (P = 0.014; relative risk = 1.97). An increased frequency of *A2* in the patients was again observed with a relative risk (1.40) similar to that found previously (*6*), but the difference did not attain statistical significance (P = 0.117). For the first time it was shown that the increased risk for NPC among the Singapore Chinese was restricted to the co-occurrence of *A2* and *Sin 2* (P = 0.007; relative risk = 2.23). The most likely explanation was that the risk for NPC was associated with the *A2–Sin 2* haplotype. Since the *A2–Sin 2* haplotype was in linkage disequilibrium in normal Chinese (*3*) and in NPC-negative controls (*4*), this explanation has implications for

TABLE 4.—*Joint occurrence of* HLA–A2 *and* Sin 2 *among Chinese NPC-positive and -negative subjects by dialect group*[a]

Antigen	NPC positive			Antigen	NPC negative		
	Sin 2	Non-Sin 2	Total		Sin 2	Non-Sin 2	Total
Cantonese[b]							
HLA–A2	22	19	41	HLA–A2	8	11	19
Non-HLA–A2	1	18	19	Non-HLA–A2	2	9	11
Total	23	37	60	Total	10	20	30
Hokkien and Teochew[c]							
HLA–A2	23	21	44	HLA–A2	5	14	19
Non-HLA–A2	4	22	26	Non-HLA–A2	3	21	24
Total	27	43	70	Total	8	35	43
Total Chinese[d]							
HLA–A2	45	40	85	HLA–A2	13	25	38
Non-HLA–A2	5	40	45	Non-HLA–A2	5	30	35
Total	50	80	130	Total	18	55	73

[a] Chi-square = 6.47; P < 0.01 (one sided); relative risk = 2.4.
[b] Frequency of A2-Sin 2 = 36.7% of NPC positive and 26.7% of NPC negative.
[c] Frequency of A2-Sin 2 = 32.9% of NPC positive and 11.6% of NPC negative.
[d] Frequency of A2-Sin 2 = 34.6% of NPC positive and 17.8% of NPC negative.

the biologic significance and the molecular mechanism of the *histocompatibility locus A* association with NPC. Some aspects of the implications already have been discussed (*1*).

Typing of *histocompatibility locus A* in 43 Malaysian Chinese with NPC confirmed the main findings of the Singapore patient study. The frequencies of *A2* and *Sin 2* in the Malaysian Chinese were comparable with those in the Singapore patients (72.1 and 60%, and 34.9 and 40%, respectively). Similarly, frequencies of joint occurrence of *A2–Sin 2* among the combined Cantonese and Hokkien–Teochews were of the same order (30.2 and 36.8%, respectively). As the main purpose of the Malaysian study was to augment the number of Chinese with NPC, no attempt was made to include a group of NPC-negative subjects comparable with those used as Singapore controls. Therefore, it is possible that the *A2–Sin 2* phenotype frequency in NPC-negative Malaysian Chinese may have differed from that in the corresponding Singapore controls. Nonetheless, among those Singapore and Malaysian Chinese in whom dialect status was known, no significant difference in the *A2–Sin 2* phenotype frequency was observed. Furthermore, although the Hong Kong Chinese patients were a selected group, the *A2–Sin 2* frequency of 42% supports the view that the *histocompatibility locus A* profile associated with NPC is common to Asian Chinese of at least three geographic locations.

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Histocompatibility Leukocyte Antigen Patterns in Nasopharyngeal Carcinoma Cases From California[1]

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ABSTRACT—Histocompatibility leukocyte antigen (HLA)-A2 in the first locus and less than two antigens in the second locus were found to be significantly associated with an increased risk to nasopharyngeal carcinoma in Chinese. HLA-A2 in the first locus alone was responsible for the increased risk. No significant HLA patterns were found to be associated with the Caucasian population.—Natl Cancer Inst Monogr 47: 153–156, 1977.

The occurrence of cancer of the nasopharynx (NPC) varies greatly among ethnic groups. Among Caucasian populations, NPC comprises only 0.25% of all cancers, whereas in Chinese populations, it is one of the most common forms (*1–3*). The incidence rate of NPC in Chinese still is high despite long-term residence by Chinese in areas where that of the native white population is low. King and Haenszel (*4*) reported that in the United States, foreign- and native-born Chinese have a combined standardized mortality ratio (SMR) of 3,120 when compared with the white population (SMR=100). Since the incidence of NPC in Chinese populations remains high despite its rare occurrence in the native population, interest has focused on possible genetic factors in the development of NPC. Because of the possible role of immunogenetic systems, much attention has centered on the histocompatibility leukocyte antigen (HLA) system.

Previous studies (*5, 6*) implicated an HLA profile in Chinese (HLA-A2) in the first locus and less than two antigens in the second locus with an increased risk of NPC. When non-Caucasian sera were used to screen for activity corresponding to the second-locus blank, a new second-locus antigen, Singapore 2 (Sin 2), associated with a high risk of NPC was identified (*7*) and independently confirmed by Payne et al. (*8*). Recently, evidence by Simons et al. (*9, 10*) confirmed the association between NPC in Chinese and the joint occurrence of HLA-A2 in the first locus and Sin 2 in the second. However, the association was confined to the haplotype *A2-Sin2*. Taking account of dialect group, Simons et al. (*6*) extended this association to Chinese in Malaya and Hong Kong.

From results obtained from a multiphasic case-control study conducted in California, this association will be examined in American Chinese. We will also examine the HLA distribution in the Caucasian population to see whether any HLA patterns are associated with an increased risk to NPC.

MATERIALS AND METHODS

Blood samples were drawn from 76 Chinese and Caucasian patients with NPC and 97 controls. The names of 58 patients from Los Angeles County were obtained from the files of the Cancer Surveillance Program (which identifies newly diagnosed cancer cases in Los Angeles County) or the California Tumor Registry. The records of 18 Chinese patients were obtained from the San Francisco–Oakland Bay Area Cancer Registry. Histopathologic specimens were reviewed for confirmation of diagnosis. Controls were selected from persons using the same hospital or clinic as the patients. Details of the selection of cases and controls are described elsewhere (*11*). The controls were matched within 5 years of the patient's age, and for sex, race, and social class, as determined by the Hollingshead Index (*12*).

Blood samples were collected in 20-cm^3 tubes containing 357 sodium heparin (USP). Samples from Los Angeles County were taken to the Department of Surgery of the University of California at Los Angeles (UCLA), and those from San Francisco were shipped in foam containers within 24 hours to UCLA. We identified HLA's by using a panel of 115 highly select antisera defining 23 specificities in the lymphocyte cytotoxicity test (*13*).

RESULTS

Table 1 shows the age and sex distribution of the Chinese and Caucasian cases and controls.

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

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TABLE 1.—*Age and sex distribution of NPC cases and controls*

Ages, yr	Chinese						Caucasian					
	Cases			Controls			Cases			Controls		
	Male	Female	Frequency	Male	Female	Frequency	Male	Female	Frequency	Male	Female	Frequency
20–29	0	1	1	0	2	2	1	1	1	1	0	1
30–39	3	4	7	6	3	9	0	0	0	4	0	4
40–49	9	3	12	8	4	12	6	0	6	5	2	7
50–59	5	2	7	12	3	15	7	7	15	11	8	19
60–69	4	3	7	2	1	3	9	4	13	6	5	11
70–79	2	1	3	5	2	7	3	0	3	3	1	4
≥80	0	0	0	0	0	0	1	0	1	2	1	3
Total	23	14	37	33	15	48	27	12	39	32	17	49
Sex ratio	1.64			2.2			2.25			1.88		
Mean age	50.7			51.0			56.9			57.0		

The mean ages of the Chinese cases and controls were comparable (50.7 vs. 51.0 yr) as were the mean ages of the Caucasian cases and controls (56.9 vs. 57.0 yr). The sex ratio of the Chinese cases was slightly lower (1.64) than that of the Chinese controls (2.20). The sex ratios of the Caucasian cases and controls were comparable (2.1 and 1.9, respectively). Ninety-two percent of the Chinese cases and 77% of the controls were born outside of the United States. Of all Chinese foreign-born cases and controls, 90% were born in the Chinese province of Kwangtung. Most of those not born in Kwangtung had parents who were born in that province. Thus the Chinese study population was considered as being Cantonese in subsequent analysis. Most of the Caucasian cases (88%) and controls (86%) were born in the United States.

The frequencies of the HLA's and their phenotype and genotype frequencies are given in table 2. At the first locus, a significant excess of HLA-A2 was found among the Chinese cases in comparison with the controls ($P<0.05$). A significant deficit of *HLA-A11* also occurred among the Chinese cases ($P<0.05$). Among the Caucasian population, only *HLA-A1* occurred significantly more frequently in cases than in controls ($P<0.05$). In the second locus, the only significant differences occurred among the Caucasian sample. In the cases, *HLA-A13* occurred more frequently ($P<$ 0.05) and *HLA-A14* occurred less frequently ($P<0.05$). However, if the number of HLA antigens tested was taken into account, only the excess of HLA-A2 among the Chinese cases remained significant.

As expected from earlier studies, HLA-A2 in the first locus and less than 2 antigens in the second locus together occurred more frequently in Chinese cases and controls ($P=0.0003$); the haplotype *A1-8* was also in linkage disequilibrium ($P=0.0001$) in Caucasian cases and controls as expected. The haplotype *A1-8* in Caucasians was not associated with a high risk of NPC [those with *A1-8* vs. those without *A1-8*: relative risk (RR) = 1.85, P = 0.2249]. On the other hand, having A2 and less than 2 antigens in the second locus was associated with a high risk of NPC in Chinese (A2-blank vs. no A2-blank: RR=3.53, $P=0.0062$). When the number of antigens in the second locus was taken into account, the presence of A2 was still significantly associated with a high risk of NPC (RR=3.40, $P=0.0209$), whereas the condition of having less than 2 antigens, after allowing for the presence of A2, did not relate to an increased risk to NPC (RR=1.68, $P=0.2345$) (table 3). Thus the presence of A2 in the first locus was sufficient to increase the risk to NPC.

DISCUSSION

The distribution of HLA's in the Chinese and Caucasian populations in this study does not differ greatly from those in the past. A comparison of our 37 Chinese cases with the 144 Chinese patients from the study of Simons et al. (*7*) from southeast Asia showed little variation. The distribution of HLA's in Caucasian controls was compatible also with a representative distribution of a normal Caucasian population reported by Simons et al. (*7*).

The haplotype *A2*-blank in the Chinese was associated significantly with an increased risk to NPC. Further stratification showed that *A2* alone was responsible for the association. These results are compatible to the results of Simons et al. (*7*) dealing with the association of HLA-A2-blank and NPC. The frequency of HLA-A2-blank among the Singapore Chinese and controls is

TABLE 2.—*Antigen, phenotype, and genotype frequencies of HLA's*

Loci	Chinese						Caucasian					
	37 NPC cases			48 controls			39 NPC cases			49 controls		
	N[a]	P[b]	G[c]	N	P	G	N	P	G	N	P	G
Locus 1												
1	0	0.0	0.0	2	4.2	2.1	20	51.3	30.2	14	28.6	15.5
2	28	75.7	50.7	20	41.7	23.6	12	30.8	16.8	23	46.9	27.2
3	0	0.0	0.0	1	2.1	1.0	7	17.9	9.4	11	22.4	11.9
9	2	5.4	2.7	4	8.3	4.3	3	7.7	3.9	6	12.2	6.3
10	2	5.4	2.7	4	8.3	4.3	4	10.3	5.3	7	14.3	7.4
11	13	35.1	19.5	26	54.2	32.3	6	15.4	8.0	3	6.1	3.1
24	3	8.1	4.1	10	20.8	11.0	7	17.9	9.4	2	4.1	2.1
28	2	5.4	2.7	0	0.0	0.0	2	5.1	2.6	7	14.3	7.4
29	0	0.0	0.0	2	4.2	2.1	6	15.4	8.0	4	8.2	4.2
30	2	5.4	2.7	2	4.2	2.1	4	10.3	5.3	6	12.2	6.3
32	0	0.0	0.0	1	2.1	1.0	3	7.7	3.9	1	2.0	1.0
Locus 2												
5	2	5.4	2.7	8	16.7	8.7	6	15.4	8.0	6	12.2	6.3
7	0	0.0	0.0	2	4.2	2.1	9	23.1	12.3	14	28.6	15.5
8	0	0.0	0.0	0	0.0	0.0	8	20.5	10.8	8	16.3	8.3
12	4	10.8	5.6	1	2.1	1.0	11	28.2	15.3	16	32.7	17.9
13	4	10.8	5.6	10	20.8	11.0	3	7.7	3.9	0	0.0	0.0
14	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	6	12.2	6.3
15	6	16.2	8.5	12	25.0	13.4	5	12.8	6.6	3	6.1	3.1
16	7	18.9	10.0	5	10.4	5.4	6	15.4	8.0	4	8.2	4.2
17	4	10.8	5.6	8	16.7	8.7	3	7.7	3.9	3	6.1	3.1
18	0	0.0	0.0	0	0.0	0.0	3	7.7	3.9	3	6.1	3.1
21	2	5.4	2.7	0	0.0	0.0	1	2.6	1.3	3	6.1	3.1
22	0	0.0	0.0	3	6.3	3.2	2	5.1	2.6	3	6.1	3.1
27	1	2.7	1.4	1	2.1	1.0	3	7.7	3.9	3	6.1	3.1
50	2	5.4	2.7	8	16.7	8.7	6	15.4	8.0	9	18.4	9.6
60	15	40.5	22.9	13	27.1	14.6	6	15.4	8.0	7	14.3	7.4

[a] N=frequency of HLA.
[b] P=phenotype.
[c] G=genotype.

TABLE 3.—*Risk ratios for NPC by occurrence of HLA-A2 and/or the presence of less than two antigens in second locus*

Antigens	No. of cases	No. of controls	Relative risk	*P*
HLA-A2 and <2 antigens	20	12		
Not (HLA-A2 and <2 antigens)	17	36	3.53	0.0062
<2 antigens				
HLA-A2	20	12		
No HLA-A2	2	4	3.33	
2 antigens				
HLA-A2	8	8		
No HLA-A2	7	24	3.43	
			3.40[a]	0.0209
HLA-A2				
<2 antigens	20	12		
2 antigens	8	8	1.67	
No HLA-A2				
<2 antigens	2	4		
2 antigens	7	24	1.71	
			1.68[a]	0.2345

[a] *Value* represents combined relative risk.

similar to that of the Chinese and controls in this study (52.8% of the Singapore vs. 54.1% of the United States cases; 29.2% of the Singapore vs. 23.5% of the United States controls). Stratification of their data also showed that having *A2* alone will increase the risk to NPC (RR=1.87, *P*=0.004). Since the second locus was not screened for the antigen Sin 2, it is difficult to draw any conclusions regarding the association between the Chinese HLA-A2 profile (A2, Sin 2) and NPC that was reported in later studies. However, at a similar stage, the data from this study conducted among Chinese living here strongly agree with results from the study conducted by Simons et al. in southeast Asia.

No significant HLA patterns were associated with the Caucasian population. However, HLA-A1, one of the more common antigens in the first locus in Caucasians, was also associated, though not significantly, with an increased risk to NPC. This association was independent of the antigens expressed in the second locus.

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Breast Cancer Among American Japanese in the San Francisco Bay Area[1]

John E. Dunn, Jr., *M.D.*[2]

ABSTRACT—The Japanese-American population was particularly well suited for the study of cancer occurrence because: 1) An American-born population as well as the immigrant Japanese-American population could be studied; 2) good cancer incidence and mortality data from Japan could be compared with data from the United States; and 3) some differences in the rate of occurrence of several specific cancer sites in Japan as compared with the United States were striking. The most significant of these involved the gastrointestinal tract and sex organs. Data were presented concerning cancer incidence rates for the Japanese-American population of the San Francisco Bay area. The high gastric rates for the Japanese in Japan were reduced in a stepwise fashion in the immigrant Japanese-American population to the American-born Japanese who were approaching the low rate of the United States. Colon cancer rates, which were low in Japan, approached the rates in the United States in both the immigrants from Japan and in Japanese Americans. The low rates of cancers of the breast, uterine corpus, and ovary of Japanese women in Japan and for prostate cancer among men rapidly approached the higher rates for these cancer sites that existed in the United States. A study of nutritional factors related to the increase in cancer of the breast in Japanese Americans is being conducted.—Natl Cancer Inst Monogr 47: 157–160, 1977.

The Japanese population of California rapidly is becoming identified with United States nativity. At the time of the 1970 census, 77% of the California Japanese were born in the United States and only 23% were foreign born. In text-figure 1, the age distribution of the California Japanese is shown by sex and nativity. The population over age 60 still is predominantly foreign born. The foreign-born female population from 20 to 50 years of age is composed largely of Japanese women who married American men serving with the army and other governmental agencies in Japan.

The American Japanese comprise a particularly important population to study for cancer incidence. 1) This Asiatic racial group represents a sizable immigrant component in the United States and composes an important segment of the population in California. 2) Good incidence and mortality data for the native Japanese are available to provide base-line information for cancer occurrence among the Japanese in their homeland. 3) Striking differences are evident between the frequency of occurrence of certain specific sites of cancer for the native Japanese and the Caucasian population in the United States. 4) The sites at which cancer is occurring in the migrant Japanese and their progeny who make up the American-Japanese population are changing toward those characteristic of the United States population and away from those found in Japan.

The rates for a number of cancer sites differ significantly in Japan from those in the United States, particularly those associated with the gastrointestinal tract and the sex organs. The high rates for gastric cancer in Japan are well known. These rates undergo reduction in the American Japanese, but in a stepwise manner in association with origin. In text-figure 2, a partial reduction takes place in age-specific gastric cancer rates in the immigrant Japanese and a further reduction in the American born. In contrast, cancer of the colon, which occurs considerably less frequently in Japan than in the United States, becomes elevated to the same extent in the immigrant and American-born Japanese as indicated in text-figure 3.

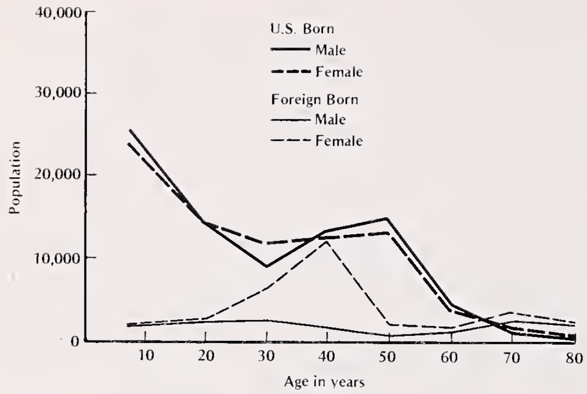
Breast cancer occurs about one-fifth as often in the women of Japan as in Caucasian women in the United States. The obvious question is: What happens to Japanese women who immigrated to the United States and their American-born progeny in regard to the occurrence of breast cancer?

In California until recently, the answer to this question could be sought only in mortality data around the decennial census years, when population data were available. Breast cancer mortality data around 1950 and 1960 indicated that mortality among Japanese in California approximated the rates in Japan more than those of the general population of women in the United States (*1*).

The Third National Cancer Survey (*2*) of 1969–71 and the continuation of cancer case-reporting by the Resource for Cancer Epidemiology (RCE) in the five counties of the San Francisco Bay Area, initiated by the Survey, provide cancer incidence data. Buell (*3*) reported that breast cancer incidence rates among American-Japanese

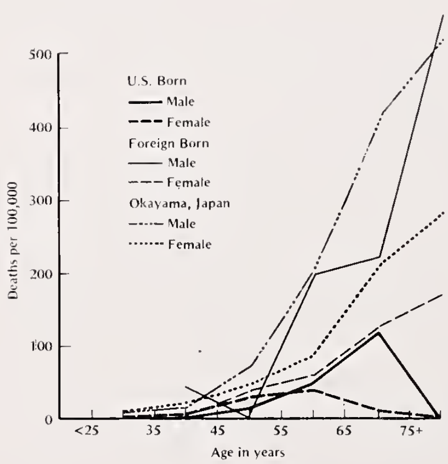
[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

[2] California Tumor Registry, 2151 Berkeley Way, Berkeley, California 94704.

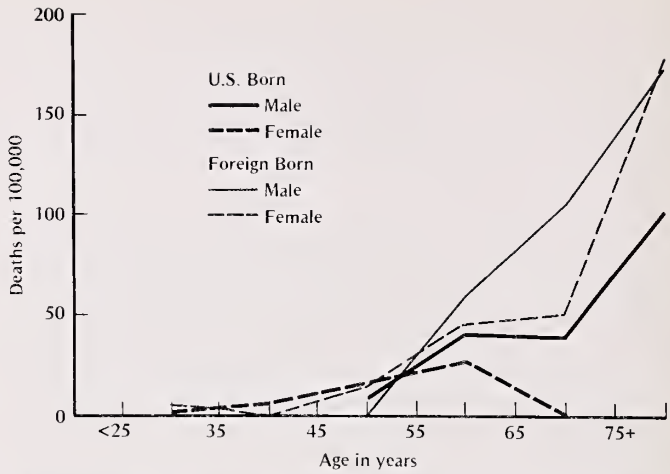


TEXT-FIGURE 1.—California Japanese by age, sex, and nativity, 1970.

women are rapidly approaching the level of occurrence among white women in the Bay Area. This is particularly true for the American-born Japanese women. Buell noted that the persistence of low breast cancer mortality among Japanese in California in 1950 and 1960 was not the experience of the Polish immigrant population who also had low breast cancer rates. Breast cancer rates in Polish women soon increased to levels comparable with other women in the United States. The Polish and Japanese migration to the United States occurred during the same time. However, almost all Polish immigrants settled in urban surroundings, whereas most early Japanese immigrants settled in rural areas. This difference in habitation might well reflect the rate of acculturation of the two migrant populations. Breast cancer mortality data have the additional bias of a survival advantage that has been found for Japanese breast cancer patients.



TEXT-FIGURE 2.—Cancer of the stomach, mortality rates/100,000: California Japanese, 1968–72, and Okayama, Japan, 1963–67.



TEXT-FIGURE 3.—Cancer of the colon, mortality rates/100,000 in California Japanese, 1968–72.

The breast cancer incidence data used by Buell have been updated in table 1 to include the period from 1969 to 1973. Observed numbers of cases among Japanese of the Bay Area are compared with expected numbers generated from age-specific incidence rates of the Prefecture of Okayama in Japan and the white population of the Bay Area. Cancers of the uterine corpus and ovary among Japanese women far exceed the number expected (based on rates from Japan). Similarly, among Japanese men, prostate cancer is much more frequent than Okayama rates would predict.

TABLE 1.—*Observed cancer cases of indicated sites among Japanese of the San Francisco–Oakland SMSA, 1969–73, compared with expected cases* [a]

Cancer site	Japanese observed cases	Expected cases	
		Okayama[b]	San Francisco–Oakland SMSA[c]
Males			
Stomach	15	63.3	9.0
Colon	11	3.2	20.3
Rectum and anus	13	5.3	10.8
Prostate	16	3.0	33.1
Females			
Stomach	18	45.0	6.2
Colon	19	4.6	23.4
Rectum and anus	7	4.8	9.7
Breast	47	13.5	82.1
Uterine corpus	13	2.2	26.1
Ovary	6	1.8	13.2

[a] Age-specified rates of Okayama, Japan, and Caucasians of the San Francisco–Oakland SMSA were used. SMSA=Standard Metropolitan Statistical Area.
[b] Data are from (*5*).
[c] Data are on file at the San Francisco Bay Area RCE.

TABLE 2.—*Observed and expected cancers of certain sites among Japanese of the San Francisco–Oakland SMSA 1969–73*

Cancer site	Age, yr			
	Under 60		Over 60	
	Observed	Expected[a]	Observed	Expected[a]
Males				
Stomach	3	2.3	12	6.7
Colon	4	5.2	7	15.1
Rectum and anus	4	3.2	9	7.6
Prostate	2	2.7	14	30.4
Females				
Stomach	4	1.8	14	4.4
Colon	6	6.8	13	16.5
Rectum and anus	3	3.3	4	9.7
Breast	41	55.7	6	26.4
Uterine corpus	11	15.6	2	10.4
Ovary	5	9.4	1	3.8

[a] Expected numbers of cases computed with age-specific white rates for San Francisco–Oakland SMSA 1969–73.

In table 2, the same data are shown separately for Japanese under and over age 60. The former are predominantly American born, whereas the latter are mostly immigrant Japanese.

A study of cancer occurrence among Japanese in Japan and migrant Japanese in the United States was undertaken over the last 10 years by Haenszel and Segi (*4*). The migrant Japanese included in the study were those living in Hawaii and California. The study was directed primarily toward cancers of the gastrointestinal tract, with the stomach and colon of specific interest. The protocol for the study included a detailed dietary history of specific Japanese food items as well as Western foods they could obtain.

The collection of Japanese cancer cases for the case-control study posed different problems in Hawaii and California. The compact insular nature of Hawaii, the large Japanese component of the Hawaiian population, and the small number of hospitals serving the whole island population simplified case identification. In California, on the other hand, the Japanese are a small component of the total population and are widely dispersed over the State. Cancer patient identification could not be complete because of the hundreds of hospitals (over 600) and lack of a cancer-reporting system, such as we now have in the Bay Area and in the Los Angeles area (through the joint efforts of the Los Angeles County Health Department and the University of Southern California). To select hospitals serving the greatest number of Japanese, our only recourse was to review death records of California Tumor Registry hospitals and others in areas heavily populated by Japanese people. We arranged for the selected hospitals to give our interviewers access to patient medical records so data on Japanese patients with cancer could be obtained. With so much effort required to locate our subjects, we did not limit ourselves to collaborative study sites but interviewed most Japanese cancer patients, regardless of site. Breast cancer patients were of particular interest.

The collaborative Japanese cancer study was terminated with the establishment of the RCE in 1972. Japanese breast cancer patients identified subsequently in the Third National Cancer Survey (*2*) and by the RCE incidence systems have been interviewed. The interviewing that had been taking place in Los Angeles was reactivated through the cancer surveillance system operated at the University of Southern California by Dr. B. E. Henderson.

Because of the illness and untimely death of Mr. Philip Buell, the study of Japanese women with breast cancer that he so diligently initiated was not pursued with the same degree of interest. It was also stymied by a young activist group of the Japanese community who felt that the Japanese people were being exploited without their thorough knowledge and consent. The information letters, consent forms, and content of the questionnaire were modified to satisfy those legitimate objections that did not jeopardize the study. Interviewing has been resumed.

The questionnaire includes a preliminary self-evaluation by the interviewee of the general characteristics of her daily food intake. Each meal is characterized as being composed of Japanese foods, Western foods, or mixed. The times of reference were for the period prior to illness and for the time around 1940 (prior to World War II). In addition, questions are posed regarding consumption of specific food items during these same periods.

We have made only a preliminary examination of data from the Japanese breast cancer study. At this time, I can only make some general comments, which indicate anticipated findings. In regard to meal characterization, both migrant and American-Japanese women now are generally contaminated by considerable exposure to Western foods. Practically all have two meals of Western food or mixed Western and Japanese food daily. At most, only one meal a day is Japanese style. A superficial comparison between Japanese breast cancer patients and controls does not indicate any striking differences in the distribution of

these meal patterns. Where a whole population is undergoing cultural and life-style changes, it is not possible to distinguish the changes responsible for any difference in disease frequency between cases and controls.

In the course of conducting the breast cancer study and identifying Japanese cases and controls at the Oak Knoll Naval Medical Research Center, we discovered an interest in endocrinologic patterns and their possible relationship to breast cancer. Dr. Norman Takaki is studying estrogen metabolism among Japanese female dependents. In some instances among mixed marriages, Japanese food is preferred by the spouse and/or the wife. Potential study subjects will be screened for those eating predominantly Japanese or Western foods, and those selected for one or the other preference will be interviewed. The endocrinologic studies would concentrate on 2 groups, 1 representing those consuming Western foods primarily and the other still preferring Japanese foods.

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Breast Secretory Activity in Nonlactating Women, Postpartum Breast Involution, and the Epidemiology of Breast Cancer[1, 2]

Nicholas L. Petrakis, *M.D.*[3]

ABSTRACT—We found an association between the secretory activity of the nonlactating breast and genes related to apocrine function. Based on these findings, we developed a biologic model that relates epidemiologic evidence for an association of reproductive experience with risk of breast cancer to our findings of genetic variation of breast secretory activity and the fact that exogenously derived substances are secreted into breast fluid. The turnover rate of secreted substances was a primary determinant of exposure of the breast epithelium to environmental and endogenous carcinogens and promoters.—Natl Cancer Inst Monogr 47: 161–164, 1977.

A genetic trait that has been subject to intensive epidemiologic and biochemical investigation in our laboratory provides some clues to the interaction of possible genetic, endocrine, and environmental influences in breast cancer etiology. Several years ago, Petrakis (*1*) reported an association between the frequency of wet-type cerumen and world breast cancer mortality. This association, at first considered implausible, had an anatomic rationale in that the ceruminal glands, certain sweat glands, and mammary glands are structurally of the apocrine type and share many biochemical characteristics. Ceruminal types are characterized phenotypically as wet and dry and are inherited in a simple Mendelian fashion, in which the allele for wet-type cerumen is dominant over that for dry. The heterozygous wet phenotype cannot be distinguished morphologically from the homozygous wet type (*2*). Dry cerumen is homozygous recessive and is markedly prevalent in Oriental and American Indian populations. The wet type predominates in populations of European and African origin. Intermediate frequencies of wet and dry alleles are found in eastern Europe, the Middle East, and South Asia (*3*). Previously, we noted the association of the wet gene with breast cancer mortality rates. In a study of Japanese women in California, I found wet-type cerumen to be twice as frequent in patients with breast cancer as in controls. Unfortunately, this association was not substantiated in a larger study of Chinese women in Hong Kong by Ing et al. (*4*). Therefore, if an association does indeed exist between wet cerumen and breast cancer, it must be an indirect one.

During the past 2 years, we have been studying the secretory activity of the nonlactating female breast as determined by nipple aspiration with a breast pump (*5*). A striking association between cerumen type, race, age, and breast fluid secretion was demonstrated. The highest proportion of breast fluid secretors (as determined by standardized nipple aspiration of fluid) was among Caucasian women, and the lowest among Oriental and American Indian women. In all groups, the proportion of breast fluid secretors declined after menopause but was most marked in Chinese and Japanese in whom only a small proportion yielded fluid at any age. This decline was parallel to that of estrogen secretion by the ovaries after menopause. In contrast, over half the postmenopausal Caucasians excreted fluid.

A significant increase in the frequency of secretors was found in Oriental women with wet as compared with those with dry cerumen, which suggested that the alleles that determine cerumen type also may influence secretory activity of the breast. A similar association was reported between cerumen type and axillary apocrine secretions by Yamashita (*6*) and other Japanese writers, in which individuals with dry cerumen had a sparsity of apocrine sweat glands and scant secretions.

These findings of secretory activity in nonparous women, the striking differences in secretory frequency between Caucasian and Oriental women, and the association of wet and dry cerumen and breast fluid-secretor status in Oriental women may be relevant to epidemiologic studies of the etiology of breast cancer, the rates of which are approximately six times lower in Oriental countries than in Western ones. Recent studies (*7*) suggest that incidence rates of breast cancer among Oriental women in Hawaii and

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[3] G. W. Hooper Foundation, University of California School of Medicine, San Francisco, California 94143.

California are increasing, but they are significantly lower than the Caucasian rates. Several hypotheses to explain these differences include the adoption of American diets (which influence sexual maturation and hormone activity), additional exposure to environmental carcinogens in the United States, and genetic admixture (*8*).

The results of our current studies suggested that both genetic and environmental factors may interact to determine breast cancer risk among Oriental women. We proposed a working hypothesis that the lower cancer risk in Oriental women may be related to an overall decrease in secretory activity of the nonlactating breast that is especially marked in those women with dry cerumen. A low level of secretory activity may minimize the exposure of the breast epithelium to exogenous and endogenous carcinogens. We recently began to investigate the secretion of exogenous substances into breast fluid and found that such substances as technetium, products of cigarette smoking, e.g., nicotine and cotinine, barbiturates, and other chemical substances are secreted rapidly into the breast fluids. This process is similar to the secretory activity in lactating breasts (Petrakis NL: Unpublished observations). These findings indicate that the epithelium of the nonlactating breast can be directly exposed to ingested and inhaled chemical substances through the circulation.

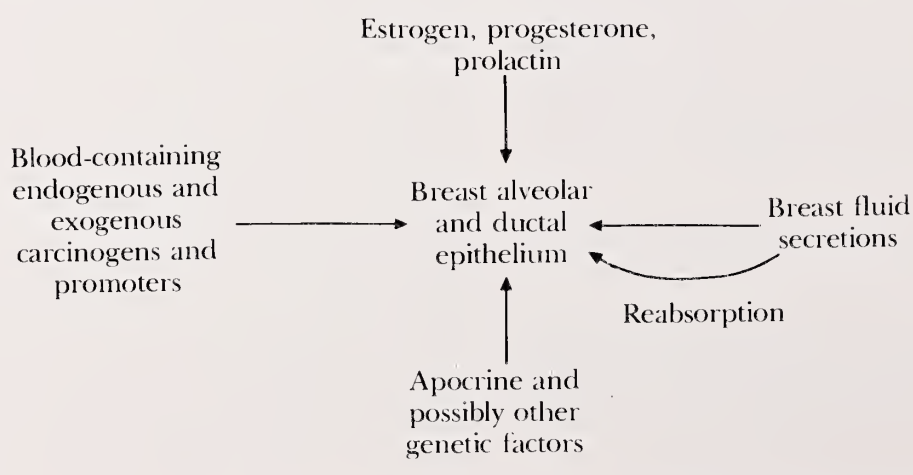
CURRENT EPIDEMIOLOGIC HYPOTHESES

This physiologic evidence of secretory activity of current epidemiologic hypotheses linking endocrine and reproductive factors to breast cancer risk may have some merit.

Studies by MacMahon and Cole (*9*) and associates (*10*), which have implicated ovarian activity in breast cancer risk, have demonstrated that women with late menarche, early natural menopause, or premenopausal oophorectomy have low breast cancer risk. They also show that breast cancer risk becomes greater as the age at which a woman bears her first child increases. Women who conceive their first children before age 18 have only one-third the breast cancer risk of those whose first pregnancy is delayed until after age 35. These findings were recently confirmed by Lilienfeld and co-workers (*11*). MacMahon and Cole (*9*) postulated that estrogen fraction variations may account for these differences.

Although estrogens may be associated with increased breast cancer risk, it is by no means certain that they play a causal role. Whereas estrogens have not been shown to be carcinogenic in humans, their effect may be indirect or permissive, with other factors having direct action. Estrogens and other hormones may act to increase cancer risk indirectly through their stimulatory actions on breast duct and alveolar-lobular development and epithelial secretory activity. The rate of breast fluid secretion and of reabsorption would determine the extent of exposure of the breast epithelium to secreted environmental and endogenous carcinogens. Thus the secretory activity of the nonlactating breast could provide the mechanisms for initiating and promoting factors acting on the epithelium to produce atypical, premalignant, and, possibly, malignant cells.

These considerations are depicted in the following diagram:



This suggestion that secreted exogenous substances may affect breast alveoli is supported by many studies in which an increase in atypical and proliferative lesions on the breast with advancing age is reported. Histologic studies by McFarland (*12*), Sandison (*13*), Symington and Currie (*14*), and more recently by Wellings et al. (*15*) indicate that by the third decade, the breast contains an increasing proportion of hypersecretory and atypical alveoli and lobules. Wellings and co-workers (*15*) noted that these lesions are especially common in nulliparous women and in women receiving medications such as digitalis, reserpine, and Dilantin. A preliminary comparison of necropsy material from Japanese women in Hawaii and in Japan indicated that hyperplasia of mammary duct epithelium and apocrine metaplasia was significantly more common in Hawaii, and the percentage of proliferative type of latent carcinoma was almost three times greater among Hawaiian Japanese (*16*). In recent studies of breast fluid cytology in our laboratory in collaboration with Dr. Eileen King (*17, 18*), we noted a marked increase in the percentage of atypical epithelial cells in women 30 to 50 years of age. It is reasonable to attribute these histologic and cytologic findings partly to secreted exogenous chemical substances.

EPIDEMIOLOGIC FEATURES OF BREAST CANCER

Based on published reports of breast development and function and on our findings of secretory activity, the epidemiologic features of breast cancer may be reexamined from the viewpoint of the hypothesis developed above. At puberty (9–12 years of age), a young girl's breast is activated into development, and secreted initiating and promoting substances have the opportunity to act on the developing breast and cause somatic mutations leading to latent cancer cells in nulliparous women. Early and late first pregnancy would have different effects on the breast that could influence the risk of cancer in this site. In the young primipara, the duct and alveolar cellular death associated with the more severe engorgement and milk-stasis regression would lead to a random loss of many of these latent cells and would have the effect of reducing the number of latent tumor cells in the breast postpartum. Simultaneously, the secretion of colostrum and milk would remove relatively static harmful secretions that have accumulated in the ducts since the onset of puberty. In the nulliparous women, one could expect that atypical, abnormal, and latent cells would accumulate in the duct and gland system with advancing age, which could lead to a higher risk of cancer than in the young primipara. The significantly increased risk in older primiparas may be due to the accumulation of mutant cell clones as a result of exposure to secreted environmental carcinogens (similar to nulliparous women) *plus* the endocrine stress of pregnancy acting on abnormal and latent cancer cells. In the older primipara, the process of engorgement milk stasis is less effective in its involuting activity, and, due to the stimulatory effect of pregnancy hormones, might result in a marked increase in abnormal cells. After regression, these breasts would contain a much greater proportion of latent cancer cells than the mammary glands of nulliparous or early primiparous women, resulting in a greater risk of breast cancer in the older primipara.

NATURAL EXPERIMENT WITH BOAT WOMEN

Recent epidemiologic studies may give additional clinical support for the hypothesis that exogenous carcinogens may be secreted into the human breast leading to increased risk of breast cancer. This work, based on a "natural experiment" in the boat women of Aberdeen in Hong Kong, was conducted by my colleague Dr. Roy Ing with the support of Dr. J. H. C. Ho of the Queen Elizabeth Hospital (Ing, R: Personal communication). By cultural tradition, the boat women nurse their infants from their right breasts only! More than 90% of them over 35 practice this custom; however, the younger boat women have abandoned this tradition. The original reasons for this peculiar custom are unknown. "We do it this way," is commonly given as a reason by the women. One possibility is that traditional Chinese dresses button on the right side, making the right breast more accessible than the left. Ing found 43 cases of breast cancer in boat women in the records of Queen Elizabeth Hospital during the past 20 years. Thirty-four breastfed their babies; one did not. No record of which breast was used was available for 2 women, and 6 were nulliparous. In the group of 34 who did breastfeed, 23 cancers occurred in the left and 11 in the right, a ratio of 2:1. In women over 55 years of age, 14 cancers occurred in the left and 4 in the right breast, a ratio of 3:1. In 1,935 nonboat Chinese women (living in Hong Kong) who had cancer of the breast and who were seen during the same period, the ratio of left to right was 1:1, which indicated no excess risk for the left or the right breast.

However, I want to reemphasize that the process of proliferation and involution of breast tissues during pregnancy may provide protection regardless of length of lactation. Dr. Ing currently is seeking further definitive information on the epidemiology of breast cancer and lactation experience in this ethnic group in Hong Kong.

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Diet and Exogenous Estrogens in Three Populations at Different Levels of Risk for Breast Cancer [1,2]

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ABSTRACT—A case-control study is being conducted in which a questionnaire is used to collect information on past history of drug usage (including menopausal estrogens) and the normal weekly dietary intake. Breast cancer cases from 3 selected populations (ages 45–74) are identified: 1) the Caucasians in Hawaii, at high risk for breast cancer; 2) the Japanese in Hawaii, at intermediate risk; and 3) the Japanese in Fukuoka, Japan, representing a low-risk population. For each case, a neighborhood and hospital control matched by race and age is interviewed. Attempts are made to verify the drug history with the subject's personal physician, and a subsample of the study population received a repeated dietary interview to assess its reliability. Pathologic slides of the breast cancer cases are reviewed by three consulting pathologists to confirm cancer diagnosis and to identify possible histologic differences in the 3 populations. In all, 200 cases and 400 controls will be interviewed from each study population.—Natl Cancer Inst Monogr 47: 165–167, 1977.

In the past, reports on the relationship of dietary factors to breast cancer in humans have been limited primarily to geographic correlation studies. Lea (*1*) observed that in various countries, the death rate for cancer of the breast was highly correlated with the per capita consumption of fat. More recently, Armstrong and Doll (*2*) noted that breast cancer incidence by countries was correlated with intake of total fat and animal protein. Hems (*3*) reported that fat consumption was more strongly associated with breast cancer mortality rates for females 65–69 than for those 40–44 years old in different countries. Although these correlation studies suggest that breast cancer may be associated with dietary intake of fat and perhaps animal protein, more direct analytical studies are needed to confirm these observations and to identify more specific dietary factors that may be related to the occurrence of breast cancer.

The use of menopausal estrogens may be another important risk factor for the development of breast cancer. Although women have taken these estrogens for more than 25 years, their carcinogenic potential for the human breast has not been thoroughly investigated. Several observers (*4, 5*) assumed that the "lack of an epidemic" of breast cancer since the introduction of exogenous estrogens attests to their safety. Two hospital-based case-control studies seem to support this impression. Doctors at The Johns Hopkins Hospital (*6*) observed that the patients with breast cancer and their matched controls had similar histories of estrogen use. In the Boston Collaborative Drug Surveillance Program, almost the same percentage of estrogen use was found among cases and controls (*7*). Although these studies suggest that no association between breast cancer and the use of estrogen may exist, further clinical research is needed to confirm this preliminary observation, especially in view of the reports on animals that support the presence of a positive association (*8, 9*).

CASE-CONTROL STUDY

In July 1975, a case-control study was begun to determine whether breast cancer is associated with specific dietary factors and the use of menopausal estrogens. Three Pacific Basin populations at different levels of risk for breast cancer are being investigated: the Japanese in Japan and the Japanese and Caucasians in Hawaii. Table 1 shows that the Japanese in Miyagi Prefecture have a low and the Caucasians in Hawaii have a high incidence of breast cancer, whereas the Japanese in Hawaii are in an intermediate position (*10*). This study will involve the Japanese in Fukuoka Prefecture instead of Miyagi, Japan, because most of the Japanese in Hawaii originated from Fukuoka or neighboring prefectures in the western part of Japan. The 1960–64 breast cancer incidence rate for Fukuoka was estimated to be 10/100,000 women/year when the age-adjusted breast cancer mortality ratio between Fukuoka and Miyagi (*11*) was applied to the incidence rate of Miyagi given in table 1.

Conducting this investigation in 3 study groups that are at different levels of risk for breast cancer provides several advantages. 1) If all 3

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[2] Supported by Public Health Service contract N01 CB53884 with the Division of Cancer Biology and Diagnosis, National Cancer Institute, Bethesda, Maryland 20014.

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TABLE 1.—*Annual age-adjusted incidence rates of breast cancer in women, by race and region, 1960–64* [a]

Race and region	Incidence/100,000
Japanese, Miyagi	11
Japanese, Hawaii	23
Caucasian, Hawaii	63

[a] Data are from Doll et al. (*10*).

groups manifest the presence or absence of an association of breast cancer with estrogen use, the significance of the finding will be strengthened. 2) Because the 3 groups consume different as well as similar food items, it may be possible to determine which items may be related to breast cancer. 3) An attempt can be made to identify risk factors that contributed to the increase of breast cancer incidence in the Japanese in Hawaii as compared with their counterparts in Japan.

In this case-control study, cases will be identified from the seven larger hospitals on the Island of Oahu and from four in Fukuoka Prefecture of Japan. We have estimated that during a 5-year period in Hawaii and a 3-year one in Fukuoka, we will have approximately 200 cases in each study group. The specific requirements for a case are: 1) Japanese or Caucasian women, age 45–74; 2) resident of Island of Oahu or Fukuoka Prefecture; 3) histologic diagnosis of a primary malignant neoplasm of the mammary gland; 4) negative history of breast cancer.

Each case will have a neighborhood and a hospital control matched by race and age within 5 years. Hospital controls will be randomly selected from women who were hospitalized at about the same time as the case and who were discharged with certain medical or surgical conditions.

COLLECTION OF DATA

For the actual collection of data, trained interviewers will administer a 12-page questionnaire designed to take approximately 50 minutes. The subjects will be shown samples of specific estrogenic preparations and asked if they have ever taken any of them or any other estrogen preparation. Each participant will also be shown samples of other medications and will be asked if she has taken any other prescribed medication in the past 10 years. This method is used because we want 1) to mask our interest in estrogens; and 2) to obtain a positive history of any drug usage from the subjects, by which we hope to obtain her signed consent granting us permission to contact her physician for verification of her drug history. This is so we can confirm the history of estrogen usage for a person with a negative as well as a positive history.

For the dietary phase of the study, the interviewer will ask each subject which of 37 food items she recently ate (during a typical week). Most of these food items were selected because of their high content of animal fat or protein. Then the interviewer will record the consumption of items by frequency and amounts as shown in 20 color prints of some of the food items. To determine the reliability of the dietary questionnaire, interviewers will ask a random sample of 15% of study participants to respond again to the dietary phase of the questionnaire within 3 months of their initial interview.

For the pathology phase of this investigation, we plan to obtain from each subject representative slides, which will be reviewed by three consulting pathologists. The findings of each case will be based on the agreement of at least two pathologists. Recent comparisons of patterns between Japan and the United States (*12*, *13*) have indicated that the Japanese have more intraductal, medullary, and colloid histologic types of breast cancer and fewer tumors of small cell or invasive ductal type. If these findings are confirmed, we can then relate the pathologic findings of the Japanese in Hawaii to the other 2 groups in the study.

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Gastrointestinal Carcinoma in the Japanese of Hawaii: A Status Report[1,2]

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ABSTRACT—The primary aim of the Japan–Hawaii Cancer Study was to identify factors that could explain the changes in cancer risk experienced by Japanese who migrated to Hawaii. Many investigations were conducted in this long-term prospective study since its inception in 1971. Among the findings that relate to gastrointestinal carcinoma were the following: 1) Bowel transit time does not appear to be related to the occurrence of large bowel cancer or to any of the benign conditions with which it is associated; 2) adenomatous and hyperplastic polyps, as well as diverticula, are much more prevalent among autopsy specimens from Japanese who had lived in Hawaii than of those in Japan; 3) adenomatous polyps and diverticula are positively associated with atherosclerosis in the necropsy population in Hawaii; 4) although the incidence of the diffuse histopathologic type of gastric cancer does not differ appreciably among the Japanese in Hawaii and Japan, the migrants have a significantly lower incidence of the intestinal type of stomach cancer; and 5) case-control studies indicated that the two conditions frequently associated with gastric carcinoma, i.e., gastric ulcer and intestinal metaplasia of the stomach, are associated with high salt intakes and adherence to the traditional Japanese diet.—Natl Cancer Inst Monogr 47: 169–172, 1977.

In recent years, cancer incidence and mortality rates of the Japanese in Hawaii have been intermediate between the rates of indigenous Japanese and those of whites in the United States (*1*). Because genetic variables are probably held constant in comparisons between native and migrant Japanese, this shift in the cancer experience of the "westernized" Japanese in Hawaii strongly suggests that environmental factors play a major role in oncogenesis.

This spontaneous sociomedical experiment among migrant Japanese provides a unique opportunity to isolate specific environmental, biochemical, and pathologic variables that may be etiologically associated with different types of cancerous lesions. For this reason, the Japan–Hawaii Cancer Study (JHCS) began in 1971 in Honolulu, Hawaii, and Chokai Village, Akita prefecture, Japan, under the sponsorship of the National Cancer Institute.

THE COHORT STUDY

The cohort study is the principal component of the JHCS program. In Hawaii, the JHCS used the subjects of the Honolulu Heart study [8,006 men of Japanese ancestry who were born from 1900 through 1919 and who were examined from 1965 to 1968 on Oahu (*2*)]. Compared with Japanese men in Hiroshima and Nagasaki, the Hawaiian Japanese males are heavier and taller; have different dietary patterns (higher intake of animal fat and protein); and have higher blood cholesterol, uric acid, and hematocrit measurements (*3*). Approximately 6,800 of the men returned for a repeat examination from 1971 through 1974 and are now under surveillance in the JHCS program in Hawaii.

Medical history, particularly with respect to the gastrointestinal tract, was recorded. History of any neoplasm was sought as well as a medical history of blood relatives. Laboratory studies included electrocardiogram, anthropometric measurements, vital capacity, urinalysis, blood pressure, hematocrit, serum cholesterol, and uric acid. In addition, blood from each individual was collected for long-term storage.

A comprehensive surveillance system of this cohort of men has been maintained to identify cases of cancer as they occur in subsequent years. This surveillance is conducted by a routine review of obituary notices, death certificates, and appropriate records from all Oahu hospitals. We have three major objectives in this surveillance: 1) the identification of new cases of cancer or "precursor lesions"; 2) knowledge of deaths due to different types of cancer; and 3) appropriate pathologic findings from surgical specimens or necropsies. Surveillance of this study population has been facilitated by its residential stability and the ease with which its ethnicity and geographic boundaries can be defined. It will take 5 or more years before a sufficient number of cases will accumulate for meaningful analyses of the cohort data. In the meantime, other types of investigations have been conducted in the JHCS.

[1] Presented at the Symposium on Epidemiology and Cancer Registries in the Pacific Basin, held in Maui, Hawaii, November 11–14, 1975.

[2] These studies are a function of the Japan–Hawaii Cancer Study at Kuakini Medical Center, supported by Public Health Service contract N01 CP33216 with the Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, Maryland 20014.

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COHORT SUBSAMPLE STUDIES

Because the Hawaiian participants in the JHCS represent volunteers of specific ages in the Japanese community, subsamples can provide useful information in comparative studies with other representative groups. Several investigations were pursued with this goal in mind.

Bowel Transit Time

Burkitt (*4*) found that populations with higher rates of large bowel cancer had slower bowel transit times (BTT) than those at lower risk for this type. He hypothesized that the prolonged contact of carcinogens in the stool with bowel mucosa led to the higher incidence of large bowel cancer. Japanese men living in Hawaii have a risk similar to that of Caucasian men for the development of large bowel cancer (*5*); thus we would expect similar BTT for Caucasians and Japanese in Hawaii.

A comparison of BTT was made between 63 Japanese cohort men and 23 Caucasian male volunteers; the mean BTT was 30.8 and 53.8 hours, respectively (*6*). Although these results were adjusted for differences in educational level, occupation, and stool frequency, the marked difference in the BTT between the two groups persisted. These surprising variations conflicted with Burkitt's well-known theory relating colon cancer to BTT. Subsequent BTT measurements of 29 indigenous Japanese men from Chokai Village revealed transit times similar to those for the Hawaiian Japanese men. These data substantiated the conclusion that changes in patterns of gastrointestinal disease are *not* related to BTT.

Fecal Bile Acids and Neutral Steroids

Hill et al. (*7*) postulated the following hypothesis for the etiology of colon cancer:

1) The composition of the gut flora depends on the nature of the diet and, in particular, on the amount of dietary fat.

2) The amount of dietary fat also determines the amount of biliary steroids (cholesterol and bile-salt degradation products) in the colon.

3) The intestinal flora are able to produce carcinogens in the colon from biliary steroids.

This hypothesis was based on the observation that stools from residents of two countries with high colon cancer rates (44 in England and 36 in the United States) showed a higher proportion of metabolically active anaerobic bacteria and a greater degree of degradation of biliary steroids than stools from residents of three countries with low colon cancer rates (11 in Uganda, 18 in Japan, and 18 in India).

Hill et al. (*7*) also found that bile acids were degraded to a greater extent in the British and Americans. It is of utmost importance that this finding can be confirmed, because degradation products (i.e., deoxycholic acid) of bile acids may be either carcinogenic (*7*) or cocarcinogenic (*8*). For example, deoxycholic acid can be converted to the potent carcinogen 20-methylcholanthrene, but only in high-temperature in vitro experiments.

The JHCS provides a unique opportunity to test the hypothesis of Hill et al. (*7*). Because the incidence of large bowel cancer in the migrant Hawaiian Japanese is higher than that in indigenous Japanese (*1*), we would expect their fecal chemistries to differ. Therefore, we decided to compare the neutral steroid and bile acid components of feces from Hawaiian Japanese and native Japanese men.

Fecal specimens from Hawaiian-born Japanese and native Japanese donors for bile acid analyses were collected and delivered to Dr. H. Mower of the University of Hawaii School of Medicine. Each sample was weighed and homogenized, and an aliquot was placed in liquid nitrogen for long-term storage. The remaining portion was analyzed for water content, total fiber, total bile acids, and lithocholic, deoxycholic, cholic, and chenodeoxycholic acids, and eight unknown bile acid components.

Preliminary findings show a difference in the prevalence of unknown bile acids between the two study groups.

Detection of Mutagenic Substances in Human Feces

Recent techniques (*9, 10*) have been developed to measure mutagenic substances in biologic fluids by a bacterial mutagen assay. Most known carcinogenic substances (80%) are active in this assay, and we believe that most mutagens detected are carcinogenic as well. When using this procedure in a preliminary study, we observed mutagens in about 15–20% of the fecal samples of Hawaiian Japanese.

This assay technique should permit the direct identification of carcinogenic substances in the fecal stream and provide a rational basis for their identification, characterization, and eventual elimination from the diet.

Bacterial Fecal Flora

As previously mentioned, intestinal bacteria

might produce carcinogens from bile steroids and variations in the incidence of colon cancer might depend partly on diet-induced differences in the composition of intestinal bacterial flora. Because differences in diet and in incidence of large bowel cancer between indigenous and Hawaiian-born Japanese have been identified, it is important that an attempt be made to characterize the composition of the intestinal flora in these two groups. W. E. C. Moore of the Anaerobic Laboratory, Virginia Polytechnic Institute, has undertaken this difficult task. He has analyzed 20 stool specimens, collected and processed anaerobically from a sample of cohort men. These data (*11*) will be used subsequently for comparison with those of other groups of people. A major difficulty in this study has been the presence of numerous fecal bacterial species, many of which have not been previously identified.

PATHOLOGIC STUDIES

Stomach Cancer

A comparative study of gastric cancer cases (407 in Miyagi Prefecture and 256 in Hawaiian Japanese) indicated that the estimated incidence rates for diffuse carcinomas were the same in both localities; however, the corresponding rates for intestinal, mixed, and other (IMO) types were substantially lower in Hawaii (*12*), as shown in table 1. The results support the hypothesis that intestinal and diffuse types of gastric carcinoma are separate entities and that the intestinal type is related to environmental factors and the diffuse type to host-related factors.

Further studies at Kuakini Hospital have suggested that a close association exists between intestinal metaplasia of the gastric mucosa and both gastric ulcer and carcinoma (*13*). Other studies have shown that intestinal metaplasia differs structurally and functionally from normal gastric and intestinal epithelium (*14*). Gastric ulcers occurred at sites in the stomach most frequently and most severely affected by both carcinoma and intestinalization. Case-control studies of this same population indicated that gastric ulcer and metaplasia are positively related to salt intake, cigarette smoking, and adherence to traditional Japanese diets (*15*).

Organ culture studies of gastric tissue from surgical specimens suggest that reepithelialization of ulcer craters is effected by actively motile cells at all stages of differentiation and that mitotic activity is suppressed during migration but increased in the intact tissues adjacent to the ulcer. Therefore, the development of carcinoma at an ulcer margin can be explained on the basis of coincidental tumor induction of metaplastic epithelium at this margin rather than of regenerating epithelium at the tumor base.

TABLE 1.—*Estimated incidence of stomach cancer per 100,000 population/yr by age, sex, and type: Miyagi and Hawaii*[a]

Age, yr	Type	Men		Women	
		Miyagi	Hawaii	Miyagi	Hawaii
15–49	IMO	15.4	5.3	6.4	1.6
	Diffuse	9.5	10.0	12.8	15.6
50–59	IMO	180.2	45.2	75.7	12.1
	Diffuse	64.6	42.2	32.4	36.5
60+	IMO	457.4	216.1	171.1	94.9
	Diffuse	83.3	109.6	66.2	48.6

[a] Data are based on incidence rates given in (*1*).

Colonic Neoplasms

Necropsy specimens of the large intestine from Hawaiian Japanese were fixed in a buffered formaldehyde solution (10% formalin) in the undistended state after rough washing and preserved in formaldehyde solution in an organ bank, according to the Stemmermann and Yatani protocol (*16*); as of 1975, we examined 202 large bowel specimens. A similar study by Drs. E. Satoh and N. Sasano of Miyagi Prefecture was performed with 293 and 187 autopsy specimens from Miyagi and Akita, respectively. The results shown in table 2 indicate that diverticula and adenomatous and hyperplastic polyps are more prevalent in the necropsy cases of Hawaiian Japanese than in their counterparts in Japan (*16*).

Hyperplastic polyps were found more often than adenomatous polyps in the sites favored by large bowel cancer in the Hawaiian Japanese; these included the sigmoid and rectosigmoid regions of the large intestine (*17*).

Ultrastructural and cell-kinetic studies of hyperplastic polyps indicated that their mode of cell renewal was the same as that of normal mucosa but with a longer turnover time and delayed migration (*18*). The fact that the superficial cells

TABLE 2.—*Percent of autopsied specimens with adenomatous polyps, hyperplastic polyps, or diverticula*

Area source	Adenomatous polyps	Hyperplastic polyps	Diverticula
Hawaii	61.0	76.0	52.0
Akita	30.0	3.0	1.0
Miyagi	19.0	2.5	0.6

TABLE 3.—*Mean vessel grade scores in autopsied cases with and without colorectal lesions*

Autopsy findings	Mean vessel grade[a]	
	Coronary	Aorta
With diverticula	3.60 (46)	4.62 (45)
Without diverticula	3.08 (20)	3.92 (24)
With adenomatous polyps	3.64 (43)	4.59 (44)
Without adenomatous polyps	3.07 (23)	4.00 (25)
With metaplastic polyps	3.46 (52)	4.43 (54)
Without metaplastic polyps	3.38 (14)	4.20 (15)

[a] Degree of atherosclerosis increases with vessel grade score. *Numbers in parentheses* indicate numbers of autopsied cases.

are longer and have more large microvilli suggested they are hypermature. If they are functionally more efficient than normal surface cells, then we might explain their site association with cancer on the basis of their ability to absorb carcinogens more effectively.

Mortality rates from carcinoma of the large intestine and myocardial infarction follow parallel trends in most populations. To determine whether the same holds true for the precursor states for these conditions, we reviewed the necropsy material from the Honolulu Heart Study. Grades of atherosclerosis of the coronary arteries and aorta, measured according to the American Heart Association panel method, were compared in subjects with and without diverticulosis, adenomatous polyps, and hyperplastic polyps (table 3). Although the number of cases is small, the findings appear to support the association of atherosclerosis with diverticula and adenomatous polyps.

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Colon and Rectum Cancer in the New Zealand Population[1]

Frank H. Foster[2]

ABSTRACT—To test the hypothesis that the high rates of large bowel cancer in New Zealand were attributable to geographic location, occupation, or country of birth, we reviewed 4,760 cases registered in that country between 1964 and 1968. Analyses demonstrated that significantly high rates existed for certain rural populations, for small subsections of the immigrant population, and for certain occupations. However, the number of persons-at-risk represented in these groups collectively were not large enough to account for the high New Zealand rates.—Natl Cancer Inst Monogr 47: 173–175, 1977.

A study of 13 populations (*1*), promoted by the International Agency for Research on Cancer (IARC), was done to determine the distribution of subsites of cancer of the large bowel. The highest rates were found in North America and New Zealand.

Subsequently, we studied three variables in the cases of large bowel cancer registered in New Zealand between 1964 and 1968 to establish whether the high rates were related to geographic region, occupation, or country of birth. Although significantly high rates were found for some of these variables, the numbers were not sufficiently large to have caused the high New Zealand rates.

Tables 1 and 2 show the number of cases of colon and rectum cancer registered between 1964 and 1968 according to sex, age, and race. The age-specific rates/100,000 are also given.

Included in the 4,760 registrations were 59 Maoris (40 colon, 19 rectum) who represented only 1.2% of the cases reviewed. In an earlier review (*2*) of Maori and non-Maori people, the crude rates for non-Maoris were at least five times higher than those for Maoris. This study confirmed this finding (*2*). However, a disproportionately high number of Maoris were diagnosed with cancer of the stomach. In 1971, of 199 total cases, 15 (7.5%) were Maoris.

The only high rate of statistical significance for colon cancer (more than 2 SD from the national mean) was for females in the Cook hospital district; all regional rates for males were within normal limits. Significantly high rates for males with rectal cancer were found for Waipawa, Waitaki, West Coast, and Taranaki hospital districts. Rates were significantly high for females living in Waitaki, Marlborough, and Palmerston North. On the basis of size of population-at-risk in these predominantly small districts, case numbers were not much greater than expected. These numbers would have contributed to, but would not have caused, the high national rates.

OCCUPATION

Table 3 groups non-Maori male colon and rectum registrations (15 years of age and over) into broad occupational groups with numbers and rates/10,000 population-at-risk in each group (population-at-risk excluding all persons not actively employed).

No rates were significantly different from the national mean. The highest was 7.5/10,000 for miners, quarrymen, and workers in similar jobs, representing 17 cases among 22,660 workers. Several specific occupations did show higher rates than others. Among colon cancer registrations were clergymen, jurists, ships' officers, coal miners, transport workers, and professional sportsmen. Among the registrations with rectal cancer, those in garment cleaning occupations, transportation, and metal work had the highest rates, as did government executives and nurses. The high rates for "other workers or those not reporting any occupation" result from the inclusion of pensioners and other retired or unemployed categories.

COUNTRY OF BIRTH

Seventy percent (3,317 cases) of the 4,760 registrations with colon and rectum cancer registered between 1964 and 1968 were born in New Zealand and 17% (801 cases) in the British Isles. Of the remainder, only Australia, with 2.4% (115 cases), accounted for more than 1.0% of total registrations.

Only those born in the British Isles were sufficiently numerous to test the hypothesis that the New Zealand high rates of colon and rectum

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[2] National Health Statistics Centre, Department of Health, P.O. Box 6314, Wellington, New Zealand.

TABLE 1.—*Cancer of colon registrations, 1964–68; numbers and age-specific rates/100,000 population*[a]

Ages, yr	Non-Maoris				Maoris			
	Males		Females		Males		Females	
	Numbers	Rates	Numbers	Rates	Numbers	Rates	Numbers	Rates
10–14	2	0.3	—	—	—	—	1	1.5
15–19	3	0.5	7	1.3	2	3.9	2	4.1
20–24	7	1.5	11	2.5	1	2.7	—	—
25–29	16	4.0	15	3.9	—	—	—	—
30–34	20	5.7	32	9.6	1	3.4	1	3.4
35–39	28	7.1	48	13.1	—	—	—	—
40–44	40	10.3	71	19.0	1	5.3	3	15.5
45–49	72	20.8	74	21.0	1	6.3	4	26.1
50–54	110	33.3	125	37.2	—	—	1	8.2
55–59	160	54.0	167	56.7	—	—	4	46.2
60–64	177	73.9	205	83.5	4	57.6	—	—
65–69	200	111.4	207	98.3	2	39.6	3	69.8
70–74	158	132.6	210	125.0	2	80.0	2	94.1
75–79	168	192.4	217	172.2	—	—	2	145.4
80–84	128	249.5	157	202.7	—	—	1	168.1
85+	74	267.6	104	224.6			2	317.5
Total	1,363	21.9	1,650	26.7	14	2.7	26	5.2

[a] Data are from a report prepared by the author for the National Health Statistics Centre, Wellington, New Zealand.

TABLE 2.—*Cancer of rectum registrations, 1964–68; numbers and age-specific rates/100,000 population*[a]

Ages, yr	Non-Maoris				Maoris			
	Males		Females		Males		Females	
	Numbers	Rates	Numbers	Rates	Numbers	Rates	Numbers	Rates
10–14	—	—	—	—	—	—	—	—
15–19	—	—	—	—	—	—	—	—
20–24	1	0.2	1	0.2	—	—	—	—
25–29	6	1.5	7	1.8	1	2.8	—	—
30–34	8	2.3	6	1.8	—	—	—	—
35–39	21	5.3	24	6.6	—	—	—	—
40–44	33	8.5	27	7.2	—	—	—	—
45–49	64	18.5	49	13.9	1	6.3	—	—
50–54	74	22.4	58	17.3	2	15.6	2	16.5
55–59	107	36.1	83	28.2	2	18.6	—	—
60–64	144	60.1	93	37.9	1	14.4	1	16.4
65–69	131	73.0	92	43.7	4	79.2	—	—
70–74	126	105.7	81	48.2	1	40.0	—	—
75–79	107	122.6	97	77.0	—	—	1	72.7
80–84	89	173.5	56	72.3	1	147.0	1	168.1
85+	52	188.0	51	110.2	—	—	1	158.7
Total	963	15.5	725	11.7	13	2.5	6	1.2

[a] *See* footnote to table 1.

TABLE 3.—*Occupational groups: numbers and rates/10,000 population of non-Maori males, aged 15 years and over*

Occupational groups	Colon		Rectum	
	No. of registrations	Rates	No. of registrations	Rates
Professional, technical and related workers	101	3.3	66	2.1
Administrators, executives, and managers	133	4.5	81	2.7
Clerical workers	125	3.9	84	2.6
Sales workers	65	2.4	41	1.5
Farmers, fishermen, hunters, loggers, and related workers	260	3.9	166	2.5
Miners, quarrymen, and related workers	17	7.5	10	4.4
Transportation and communications workers	84	3.2	71	2.7
Craftsmen, production process workers, and laborers	418	2.7	312	2.0
Service, sport, and recreation workers	55	4.0	43	3.1
Armed forces	3	0.6	7	1.4
Other workers and those not reporting any occupation	100	28.2	82	23.1
Total	1,361	3.5	963	2.4

TABLE 4.—*Expected and observed numbers of colon cancer registrations in New Zealand and the British Isles*[a]

Age groups, yr	Observed: New Zealand born		Observed: British born		Expected No. of people born in British Isles
	No.	Rate	No.	Rate	
Male					
35–44	57	9.7	1	0.8	5
45–54	139	26.3	20	19.2	101
55–64	257	64.8	45	43.0	170
65–74	244	120.5	62	89.9	182
75+	217	205.9	107	225.0	238
Total	914	17.7	235	36.2	696
Female					
35–44	82	13.9	5	5.4	32
45–54	164	29.6	17	18.3	101
55–64	259	62.7	50	54.6	226
65–74	293	111.0	83	95.3	251
75+	313	182.3	119	191.8	330
Total	1,111	21.3	274	45.3	940

[a] Values are for non-Maori only; mean annual rates:100,000 population.

tumors are associated with its immigrant population. Therefore, other national groups were not compared with the New Zealand-born population. Since more than 99% of registrants born in the British Isles were 35 years of age or over, the populations-at-risk and registrants were truncated accordingly.

In tables 4 and 5 comparisons of the age- and sex-specific rates of those born in New Zealand and in Britain for each site are given, and the expected numbers of the latter for each by standardization of the observed rates of the people born in the British Isles to the native New Zealanders at risk are shown.

TABLE 4.—*Expected and observed numbers of colon cancer registrations in New Zealand and the British Isles*[a]

Age groups, yr	Observed: New Zealand born		Observed: British born		Expected No. of people born in British Isles
	No.	Rate	No.	Rate	
Male					
35–44	39	6.6	5	4.2	25
45–54	97	18.4	16	15.4	81
55–64	180	45.4	44	42.0	166
65–74	181	89.4	42	60.9	123
75+	154	146.2	64	134.6	142
Total	651	12.6	171	38.5	537
Female					
35–44	44	7.4	1	1.1	6
45–54	75	13.5	10	10.7	60
55–64	119	28.8	25	27.3	113
65–74	108	40.9	39	44.8	118
75+	134	78.0	39	62.9	108
Total	480	9.2	114	26.8	405

[a] Values are for non-Maori only; mean annual rates/100,000 population.

If the population born in the British Isles had made a significant contribution to the high New Zealand rates, the expected number of the former registrants would have been considerably greater than the observed number of native New Zealanders. For British-born men and women aged 75 years and over, the colon cancer rates were a little higher than for those born in New Zealand, but for all other ages the rates of the former were lower. The observed colon cancer registrations of native New Zealanders were greater than those of people of British birth by 31% for males and 18% for females; this was also true for 21% of the males and 19% of the females with cancer of the rectum who were born in New Zealand.

These tables demonstrate that New Zealand's high rates for colon and rectum cancer are not attributable to a higher incidence in the immigrant population.

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GLOSSARY

ABCC	Atomic Bomb Casualty Commission
AL	acute leukemia
ATB	at time of bombing
BTT	bowel transit time(s)
CCH	Cancer Center of Hawaii
CGL	chronic granulocytic leukemia
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CO	carbon monoxide
CSP	Cancer Surveillance Program
CSS	Cancer Surveillance System
DS	disease susceptibility
EBV	Epstein-Barr virus
EDP	Epidemiology and Demographic Program
EDU	Epidemiology and Demography Unit
FA	Fanconi's anemia
FHCRC	Fred Hutchinson Cancer Research Center
FL	follicular lymphoma
GF	gene frequency
GMT	geometric mean titer
HB	hepatitis B
HD	Hodgkin's disease
HLA	human leukocyte antigen
HS	Hsieh antigen
HSVI	herpes simplex virus, type 1—oral
HSVII	herpes simplex virus, type 2—genital
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ICDA	International Classification of Diseases, Adapted
IMO	intestinal, mixed, and others (types of cancer)
JHCS	Japan-Hawaii Cancer Study
JNIH	Japanese National Institute of Health
LS	lymphosarcoma
M	myeloma
MF	myelofibrosis
MG	methylguanidine
MHC	major histocompatibility complex
MLC	mixed lymphocyte culture
NCI	National Cancer Institute
NO	nitric oxide
NOS	not otherwise specified
NPC	nasopharyngeal carcinoma
OL	other lymphomas

O/E	observed to expected ratios
PAHO	Pan American Health Organization
PAP	Papanicolaou smear
PAS	periodic acid–Schiff
PEB	Program in Epidemiology and Biostatistics
PHA	phytohemagglutinin
PV	polycythemia vera
RCE	Resource for Cancer Epidemiology
RCS	reticulum cell sarcoma
RR	relative risk; risk ratio
SEER	Surveillance, Epidemiology, and End Results
Sin 2	Singapore 2
SIR	standard incidence ratio
SMR	standardized mortality ratio
SMSA	Standard Metropolitan Statistical Area
SNOP	Systematized Nomenclature of Pathology
TTPI	Trust Territory of the Pacific Islands
UCLA	University of California at Los Angeles
VZ	varicella zoster
WHO	World Health Organization
XP	xeroderma pigmentosum

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